Review Article

Developments in targeted therapy & immunotherapy—how non-small cell lung cancer management will change in the next decade: a narrative review

Molly S. C. Li[1], Kevin K. S. Mok[2], Tony S. K. Mok[1]

[1]Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China; [2]Department of Clinical Oncology, Prince of Wales Hospital, Hong Kong, China

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Correspondence to: Molly S. C. Li. Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong, China. Email: molly@clo.cuhk.edu.hk.

Background and Objective: The adoption of targeted therapy and immunotherapy has revolutionised the treatment landscape of non-small cell lung cancer. For early staged disease, incorporation of targeted therapy and immunotherapy has recently been demonstrated to reduce recurrence. Development of targeted therapies in advanced lung cancer is driven by advanced genomic sequencing techniques, better understanding of drug resistance mechanisms, and improved drug designs. The list of targetable molecular alteration is continuously expanding, and next generation molecular therapies have shown promise in circumventing drug resistance. Lung cancer patients may achieve durable disease control with immune checkpoint inhibitors however most patients develop immunotherapy resistance. A wide spectrum of resistance mechanisms, ranging from impaired T-cell activation, presence of coinhibitory immune checkpoints, to immunosuppressive tumour microenvironment, have been proposed. A multitude of novel immunotherapy strategies are under development to target such resistance mechanisms. This review aims to provide a succinct overview in the latest development in targeted therapy and immunotherapy for NSCLC management.

Methods: We searched all original papers and reviews on targeted therapy and immunotherapy in non-small cell lung cancer (NSCLC) using PubMed in June 2022. Search terms included "non-small cell lung cancer", "targeted therapy", "immunotherapy", "EGFR", "ALK", "ROS1", "BRAF V600E", "MET", "RET", "KRAS", "HER2", "ERBB2", "NRG1", "immune checkpoint", "PD-1", "PD-L1", "CTLA4", "TIGIT", "VEGF", "cancer vaccine", "cellular therapy", "tumour microenvironment", "cytokine", and "gut microbiota".

Key Content and Findings: We first discuss the incorporation of targeted therapy and immunotherapy in early staged NSCLC. This includes the latest clinical data that led to the approval of neoadjuvant immunotherapy, adjuvant immunotherapy and adjuvant targeted therapy for early staged NSCLC. The second section focuses on targeted therapy in metastatic NSCLC. The list of targetable alteration now includes but is not limited to EGFR, ALK, ROS1, BRAF V600E, MET exon 14 skipping, RET, KRAS G12C, HER2 and NRG1. Potential drug resistance mechanisms and novel therapeutics under development are also discussed. The third section on immunotherapy in metastatic NSCLC, covers immunotherapy that are currently approved [anti-PD-(L)1 and anti-CTLA4], and agents that are under active research (e.g., anti-TIGIT, cancer vaccine, cellular therapy, cytokine and other TME modulating agents).

Conclusions: This review encompasses the latest updates in targeted therapy and immunotherapy in lung cancer management and discusses the future direction in the field.

Keywords: Non-small cell lung cancer (NSCLC); targeted therapy; immunotherapy

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Introduction

Background

Lung cancer is the leading cause of cancer death worldwide, claiming 1.8 million lives annually (1). About 85% of lung cancers are non-small cell lung cancer (NSCLC). Patients with lung cancer have dismal prognoses, due to the fact that more than half of them present with metastatic disease, and recurrence is common among those who have early-staged disease (2). Conventional cytotoxic chemotherapy only offers a modest improvement in survival for NSCLC patients (3). The identification of actionable driver oncogenes such as EGFR and ALK, and immune checkpoints such as PD-L1, have led to the development of personalized cancer care. Over the past decade, significant advances in targeted therapy and immunotherapy have transformed the treatment paradigm and survival outcomes of patients with NSCLC. Patients receiving genotype-directed therapy achieve more rapid but durable tumour responses and usually less treatment related toxicities comparing to those who receive conventional chemotherapy. Nonetheless, therapeutic resistance remains a perennial challenge and much research is dedicated to this area.

Rationale and knowledge gap

A myriad of novel therapeutic approaches has shown promise with potential to change future practice. The treatment landscape of NSCLC is rapidly evolving and turning increasingly complex. An updated review in this topic offers oncologists and other clinical practitioners a succinct overview in the state-of-the-art and future trends in NSCLC management.

Objective

This review discusses the latest development in targeted therapy and immunotherapy in NSCLC management. This review also addresses the resistance mechanisms to targeted therapy and immunotherapy and discusses future research direction in this field. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4444/rc).

Methods

On June 15th, 2022, a systematic literature search was conducted by MSC Li and KKS Mok. Final approval of literature search was conducted by MSC Li and KKS Mok. An online search of literature utilizing PubMed was employed. Selection criteria included NSCLC, targeted therapy, immunotherapy, EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, HER2, ERBB2, NRG1, immune checkpoint, PD-1, PD-L1, CTLA4, TIGIT, VEGF, cancer vaccine, cellular therapy, tumour microenvironment, cytokine, and gut microbiota from 2005 to 15th June 2022. Only studies in English were included (*Table 1*).

Early staged NSCLC

Historically, neoadjuvant and adjuvant chemotherapy only provide an overall 5% survival benefit (4,5). Motivated by the success of immunotherapy in advanced stage lung cancer (6), much research on immunotherapy has been done in the neoadjuvant or adjuvant setting in recent years to improve this statistic.

Neoadjuvant immunotherapy in surgically resectable NSCLC

The concept of neoadjuvant immunotherapy is supported by the hypothesis that an in-situ tumour may serve as a neoantigen source for stimulation of tumour-specific T-cells (7). Most neoadjuvant clinical trials evaluated pathological response rate as their major study endpoints. While overall survival is the gold standard for study endpoint in neoadjuvant studies, surrogate endpoints are needed for practicality and cost effectiveness. Pathologic response is emerging as one important endpoint because it has strong correlation to recurrence and survival (8), and is more predictive than radiologic response (9).

Earlier trials investigated neoadjuvant immunotherapy with anti-programme death-(ligand)-1 (anti-PD-L1/PD-1) monoclonal antibodies alone. They resulted in major

Table 1 Search strategy summary

Items	Specification
Date of search	15th June, 2022
Databases	PubMed
Search terms used	"non-small cell lung cancer", "targeted therapy", "immunotherapy", "EGFR", "ALK", "ROS1", "BRAF V600E", "MET", "RET", "KRAS", "HER2", "ERBB2", "NRG1", "immune checkpoint", "PD-1", "PD-L1", "CTLA4", "TIGIT", "VEGF", "cancer vaccine", "cellular therapy", "tumour microenvironment", "cytokine", and "gut microbiota"
Timeframe	2005 to 15th June, 2022
Inclusion criteria	English literature only
Selection process	Systematic literature search was conducted by MSC Li and KKS Mok. Final approval of literature search was conducted by MSC Li and KKS Mok

pathologic response rates (MPR, defined as 10% or less viable tumor in resected primary tumour) of 20–45% and pathologic complete response (pCR, defined as no viable tumour cells in resected primary tumour and lymph nodes) rates of 7–10% (7,10-12). A phase II study showed that dual immunotherapy with nivolumab and ipilimumab achieved higher MPR rate (38% versus 22%) and pCR rate (29% versus 9%) compared to nivolumab alone (12).

In general, pathological response rates with single agent immunotherapy were lower than immunochemotherapy combinations. Single arm studies testing neoadjuvant immunochemotherapy combinations reported MPR rates of 57–83% and pCR rates of 18–63%. Toxicity was understandably higher due to the addition of chemotherapy, but surgery was in general feasible (13-15).

The only published phase III trial evaluating chemo-immunotherapy to date was the CheckMate 816 trial, which compared three cycles of neoadjuvant nivolumab plus chemotherapy versus chemotherapy in stage IB (tumor size ≥4 cm) to IIIA patients (AJCC staging 7th edition) without *EGFR/ALK* alterations. The primary outcomes were met, with an event-free survival (EFS) of 31.6 months versus 20.8 months (HR 0.63, 97.38% CI: 0.43–0.91), pCR of 24% versus 2% (odds ratio 13.94; 99% CI: 3.49–55.75) in the chemoimmunotherapy versus chemotherapy arms respectively. Patients with high PD-L1 expression (HR 0.24, 95% CI: 0.10–0.61) or stage III disease (HR 0.54, 95% CI: 0.37–0.80) benefited more from the neoadjuvant immunochemotherapy combination. The trial also validated that pCR was strongly predictive of EFS (16). A number of phase III neoadjuvant immunochemotherapy studies are underway (*Table 2*).

Future studies will explore combining neoadjuvant immunotherapy with antiangiogenic drugs such as lenvatinib (NCT04875585), apatinib (NCT04379739) and bevacizumab (NCT04973293), or relatlimab (NCT04205552), an anti-LAG3 checkpoint inhibitor. Tri-modality combinations with chemotherapy, immunotherapy, and radiotherapy are also being studied (NCT04245514, NCT05157542).

Adjuvant immunotherapy in surgically resected NSCLC

IMpower010 was the first published phase III immunotherapy study in the adjuvant setting in surgically treated lung cancer, comparing adjuvant atezolizumab up to one year versus supportive care after surgery and adjuvant chemotherapy (*Table 2*). This study showed improved disease-free survival (DFS) in stage II to IIIA patients with PD-L1 ≥1% (HR 0.66, 95% CI: 0.50–0.88; 3-year DFS 60% versus 48%) and in all comers of stage II to IIIA (HR 0.79, 95% CI: 0.64–0.96; 3-year DFS 56% versus 49%). Exploratory analysis suggested that the PD-L1 expression might be related to outcome, with a HR of 0.43 (95% CI: 0.27–0.68) in the ≥50%, but 0.97 (95% CI: 0.72–1.31) in the ≤1% group (17).

Data from the second interim analysis for adjuvant pembrolizumab was presented recently. The KEYNOTE-091 study was a triple blinded phase III randomized study comparing adjuvant pembrolizumab versus placebo for stage IB (≥4 cm) to IIIA patients (AJCC staging 7th edition) after surgery with or without chemotherapy. The study reported a significant DFS benefit with pembrolizumab but unlike IMpower010, the DFS outcomes did not correlate with PD-L1 expression. The reason for this discrepancy in outcome was not clear (18). Other phase III trials testing adjuvant

Table 2 Key randomized perioperative immunotherapy studies in early staged NSCLC

Study name	Intervention	Primary endpoint	Accrual status	NCT identifier
Neoadjuvant				
CheckMate 816	Nivolumab plus platinum based chemotherapy	pCR, EFS	Results published	NCT02998528
CheckMate 77T	Nivolumab plus platinum based chemotherapy followed by adjuvant nivolumab	EFS	Recruiting	NCT04025879
KEYNOTE-671	Pembrolizumab plus platinum based chemotherapy followed by adjuvant pembrolizumab	EFS, OS	Active, not recruiting	NCT03425643
IMpower030	Atezolizumab plus platinum based chemotherapy followed by adjuvant atezolizumab	EFS	Active, not recruiting	NCT03456063
AEGEAN	Durvalumab plus platinum based chemotherapy	pCR, EFS	Recruiting	NCT03800134
	Tislelizumab plus platinum based chemotherapy followed by adjuvant tislelizumab	MPR, EFS	Recruiting	NCT04379635
	Sintilimab plus platinum based chemotherapy followed by adjuvant sintilimab	pCR, EFS	Not yet recruiting	NCT05116462
	SHR-1316 plus platinum based chemotherapy followed by adjuvant SHR-1316	MPR, EFS	Recruiting	NCT04316364
	Toripalimab plus platinum based chemotherapy followed by adjuvant toripalimab	MPR, EFS	Recruiting	NCT04158440
Adjuvant				
IMpower010	Atezolizumab (after adjuvant chemotherapy)	DFS	Results published	NCT02486718
KEYNOTE-091	Pembrolizumab (after adjuvant chemotherapy but chemotherapy not mandatory)	DFS	Results published	NCT02504372
ANVIL	Nivolumab (after adjuvant chemotherapy)	DFS, OS	Active, not recruiting	NCT02595944
BR31	Durvalumab (after adjuvant chemotherapy but chemotherapy not mandatory	DFS in PD-L1 TC ≥25%	Active, not recruiting	NCT02273375
LungMate-008	Toripalimab plus platinum based chemotherapy for 4 cycles	DFS	Not yet recruiting	NCT04772287
NADIM-ADJUVANT	Nivolumab plus carboplatin plus paclitaxel followed by maintenance nivolumab	DFS	Recruiting	NCT04564157
ALCHEMIST-IO	Arm 1: adjuvant chemotherapy alone followed by maintenance pembrolizumab Arm 2: pembrolizumab plus platinum based chemotherapy followed by maintenance pembrolizumab	DFS	Recruiting	NCT04267848
MERMAID-1	Durvalumab plus platinum based chemotherapy	DFS in MRD+ analysis set	Active, not recruiting	NCT04385368
MERMAID-2	Durvalumab	DFS in PD-L1 TC ≥1%	Active, not recruiting	NCT04642469

NSCLC, non-small cell lung cancer; DFS, disease-free survival; EFS, event-free survival; MPR, major pathological response; MRD, minimal residual disease; OS, overall survival; pCR, pathological complete response; PD-L1, programme death-ligand 1; TC, tumour cells.

PD-(L)1 blockade in patients with resected NSCLC have completed accrual and will provide additional insight into the potential biomarkers (*Table 2*). More importantly, in future, testing clinically whether there are differences in outcome between a neoadjuvant and adjuvant approach should be further pursued.

Immunotherapy in locally advanced unresectable lung cancer

Definitive chemoradiotherapy followed by consolidation durvalumab for up to 1 year is now the standard for unresectable stage III NSCLC based on the landmark PACIFIC trial (19). In the latest update, durvalumab versus placebo was associated with median overall survival (OS) of 47.5 versus 29.1 months. Patients with PD-L1 expression ≤1% or *EGFR/ALK* alteration did not yield OS benefit from the study drug [HR 1.15 (95% CI: 0.75–1.75) and HR 0.85 (95% CI: 0.37–1.97) respectively] (20).

Building upon the PACIFIC trial, the COAST trial was a phase II trial incorporating oleclumab (anti-CD73 mAB) or monalizumab (anti-NKG2A mAB), novel drugs with immunomodulatory effects, to standard consolidation durvalumab. Encouraging response rates of 30.0% (oleclumab plus durvalumab), 35.5% (monalizumab plus durvalumab), versus 17.9% (durvalumab) were reported (21). This has now moved onto a phase III study (NCT05221840).

Integrating immunotherapy into chemoradiotherapy was feasible in a phase II trial involving pembrolizumab with response rate of about 70% and Grade 3 pneumonitis of 7–8% (22). Another similar trial involving concurrent durvalumab is underway (NCT03519971). Novel immunotherapy agents such as anti-TIGIT are being investigated as a component of consolidation therapy (NCT04513925, NCT05211895) and as part of the chemoradiotherapy regime (NCT04866017).

Neoadjuvant and adjuvant therapy in NSCLC with EGFR or other driver oncogene

Neoadjuvant tyrosine kinase inhibitor (TKI) is not yet an established standard treatment for patients with NSCLC harboring driver mutation. The EMERGING-CTONG 1103 trial compared neoadjuvant erlotinib with neoadjuvant chemotherapy in stage IIIA N2 patients with *EGFR* exon 19 or 21 mutations. While objective response (54.1% versus 34.3%, P=0.09) was numerically higher and progression free survival (PFS) was statistically significantly better of 21.5 months versus 11.4 months (P<0.001), neoadjuvant erlotinib did not improve overall survival (median OS 42.2 versus 36.9 months, HR 0.83, P=0.513) (23). This trial raised an important message that PFS benefit in an neoadjuvant targeted therapy study does not necessarily translate into OS benefit. NEOS, a single arm trial of 18 patients, reported response rate of 73.3% with neoadjuvant osimertinib (24). An ongoing phase III trial called NEOADAURA will determine whether osimertinib with or without chemotherapy is beneficial in the neoadjuvant setting (NCT04351555).

The most promising data on adjuvant epidermal growth factor receptor (EGFR) TKI involved osimertinib in the ADAURA trial. This was a phase III trial in which patients with resected stage IB to IIIA NSCLC (AJCC staging 7th edition) with *EGFR* exon 19 deletion or L858R mutation were randomized to receive either up to three years of osimertinib or placebo. The reported 24-month DFS was an impressive 90% versus 44% (HR 0.17, P<0.001). Given the overwhelming DFS gain the study was unblinded early and the drug was Food and Drug Administration (FDA) approved for this indication. OS data has yet to mature (25).

Clinical data on perioperative TKI for NSCLC harboring other driver oncogenes (e.g., *ALK*, *ROS1*) is scarce due to rarity of these tumours. ALINA is an ongoing phase III study comparing adjuvant alectinib with standard platinum-based chemotherapy in patients with resected ALK positive NSCLC (NCT0456076). NAUTIKA1 is a phase II study in which patients receive genotype-directed, neoadjuvant TKI followed by surgery, adjuvant chemotherapy and 2 years of TKI (NCT04302025). Primary study outcome is MPR rate. At present, osimertinib is the only FDA approved targeted therapy for early staged NSCLC harboring a driver mutation.

Early-staged NSCLC: future direction

The phase III studies presented above have set the stage for immunotherapy and targeted therapy in early staged NSCLC. Future OS data and results of the other ongoing phase III studies will confirm the benefit of immunotherapy and targeted therapy in this setting. The classical notion that the histological subtype and molecular profile are irrelevant in early staged NSCLC management has become obsolete. *EGFR* mutation and PD-L1 expression should be tested at diagnosis to guide treatment plan. Multidisciplinary discussion is crucial for management of stage III, or even stage II NSCLC as different treatment approaches are now viable. Given the

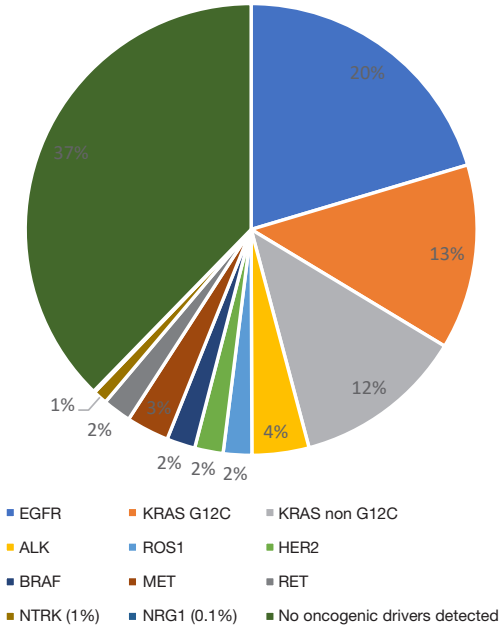

Figure 1 Prevalence of actionable driver alterations in lung adenocarcinoma. Frequency of driver oncogenes in LUADs in Caucasians, adapted from Jordan *et al.* (28). LUADs, lung adenocarcinomas.

improving response rates of neoadjuvant treatment, tumours that are determined unresectable at diagnosis may be converted to resectable. As a result, the line between unresectable and resectable tumours may blur. Future studies will also focus on identifying patients, for example those who fail to achieve pCR, or those with minimal residual disease after surgery, who will benefit from intensive treatment.

Targeted therapy in metastatic NSCLC

Overview

The foundation of targeted therapy in lung cancer is based on the knowledge that certain genetic alterations act as primary drivers of cancer formation, such that inhibition of the driver oncogene leads to cancer growth arrest and cell death. Targeted therapies in NSCLC are conventionally referred to small molecule gene-specific tyrosine kinase inhibitors. Recently, innovations in drug designs have led to development of newer classes of targeted therapies like antibody-drug conjugates (ADC) and bispecific antibodies. Tyrosine kinase inhibitors (TKIs) have proven enormous success in NSCLC treatment as up to one half of lung adenocarcinomas (LUAD) harbour a driver oncogene (26-28) (*Figure 1*). To date, there are nine oncogenes in NSCLC with FDA approved therapies.

EGFR mutation

Currently, 5 EGFR TKIs (namely erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib) are approved for treatment naïve, advanced *EGFR* mutated NSCLC (*Table 3*) (29-41). The FLAURA study randomized 556 patients with untreated advanced *EGFR*-mutated NSCLC to receive osimertinib or a first-generation EGFR TKI. Osimertinib demonstrated superiority over first-generation TKI in terms of PFS, OS, intracranial objective response rate (ORR), as well as a more favourable side effect profile, and thus is the preferred first-line treatment option for advanced NSCLC harbouring a sensitizing *EGFR* mutation (42,43).

Treatment strategy upon osimertinib resistance is under active research. The standard treatment for patients after osimertinib resistance is cytotoxic chemotherapy. With growing understanding of the resistance patterns to osimertinib and advances in drug designs, multiple new treatment approaches have shown promise.

EGFR exon 20 C797S mutation is the most common EGFR-dependent mechanism of osimertinib resistance (7–26%) and interferes with drug binding to the EGFR protein (51). Preclinical data showed that fourth generation EGFR TKIs, such as BLU-701, BLU-945, BBT-176 and JBJ-09-063, were active against C797S resistance (52-55). Phase I/II studies are now underway to study the clinical efficacy and safety of these agents (e.g., NCT 05153408, NCT04820023).

MET amplification accounts for up to 20% of osimertinib resistance (51). The combination of EGFR TKI plus a selective MET inhibitor (e.g., tepotinib, capmatinib, savolitinib) was tested in patients with MET overexpression or amplification resistance in several phase Ib/II trials. Reported ORRs were around 30–60% supporting TKI combination as a treatment option for patients with acquired *MET* dysregulation (56-59). Phase III randomized studies such as GEOMETRY-E (NCT04816214) and SAFFRON (NCT-05261399) will compare such combinations with standard platinum-based chemotherapy. EGFR TKI resistance mediated by other actionable alterations are rare but treatment success of different TKI combinations have been reported in literature (60-62), highlighting the importance of repeating genomic profiling after TKI failure to search for druggable resistance mutations.

Amivantamab is a bispecific antibody against EGFR

Table 3 Key randomized targeted therapy studies in NSCLC with actionable genomic alterations

Study name	Intervention	Comparator	Treatment line	Median PFS, months, HR (95% CI)	Median OS, months, HR (95% CI)	Ref
EGFR						
IPASS	Gefitinib	Carboplatin plus paclitaxel	1st	9.5 *vs.* 6.3, HR 0.48 (0.36 to 0.64)	18.8 *vs.* 17.4, HR 1.0 (0.76 to 1.33)	(29,30)
NEJ002	Gefitinib	Carboplatin plus paclitaxel	1st	10.8 *vs.* 5.4, HR 0.30 (0.22 to 0.41)	30.5 *vs.* 23.6, HR 0.887 (0.63–1.24)	(31,32)
EURTAC	Erlotinib	Platinum based chemotherapy	1st	9.7 *vs.* 5.2, HR 0.37 (0.25–0.54)	19.3 *vs.* 19.5, HR 1.04 (0.65–1.68)	(33)
OPTIMAL	Erlotinib	Carboplatin plus gemcitabine	1st	13.1 *vs.* 4.6, HR 0.16 (0.10–0.26)	22.8 *vs.* 27.2, HR 1.19 (0.83–1.71)	(34,35)
LUX-LUNG-7	Afatinib	Gefitinib	1st	11.0 *vs.* 10.9, HR 0.73 (0.57–0.95)	27.9 *vs.* 24.5, HR 0.86 (0.66–1.12)	(36,37)
ARCHER-1050	Dacomitinib	Gefitinib	1st	14.7 *vs.* 9.2, HR 0.59 (0.47–0.74)	34.1 *vs.* 26.8, HR 0.76 (0.58 to 0.99)	(38,39)
AURA3	Osimertinib	Platinum plus pemetrexed	2nd, progression after first-line EGFR TKI with T790M mutation	10.1 *vs.* 4.4, HR 0.30 (0.23 to 0.41)	26.8 *vs.* 22.5, HR 0.87 (0.67 to 1.12)	(40,41)
FLAURA	Osimertinib	Erlotinib or gefitinib	1st	18.9 *vs.* 10.2, HR 0.46 (0.37 to 0.57)	38.6 *vs.* 31.8, HR 0.80 (0.64 to 1.00)	(42,43)
ALK						
PROFILE-1014	Crizotinib	Platinum plus pemetrexed	1st	10.9 *vs.* 7.0, HR 0.45 (0.35 to 0.60)	NR *vs.* 47.5, HR 0.76 (0.548 to 1.053)	(44,45)
ASCEND-4	Ceritinib	Platinum plus pemetrexed	1st	16.6 *vs.* 8.1, HR 0.55 (0.42 to 0.73)	NR *vs.* 26.2, HR 0.73 (0.50 to 1.08)	(46)
ALEX	Alectinib	Crizotinib	1st	34.8 *vs.* 10.9, HR 0.43 (0.32 to 0.58)	NR *vs.* 57.4, HR 0.67 (0.46 to 0.98)	(47)
ALTA-1L	Brigatinib	Crizotinib	1st	24.0 *vs.* 11.1, HR 0.48 (0.35 to 0.66)	NR *vs.* NR, HR 0.81 (0.51 to 1.22)	(48)
eXalt3	Ensartinib	Crizotinib	1st	25.8 *vs.* 12.7, HR 0.51 (0.35 to 0.72)	NR *vs.* NR, HR 0.91 (0.54 to 1.54)	(49)
CROWN	Lorlatinib	Crizotinib	1st	NR *vs.* 9.3, HR 0.28 (0.19 to 0.41)	NR *vs.* NR, HR 0.72 (0.41 to 1.25)	(50)

NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression free survival; Ref, reference.

and c-MET (63). In the CHRYSALIS and CHRYSALIS-2 single arm phase II studies, the combination of amivantamab and lazertinib (a third-generation EGFR TKI) achieved response rates of 36% and 32% respectively in patients who progressed on osimertinib (64,65). These data supported bispecific antibody to be an alternative approach other than tyrosine kinase inhibition in targeting oncogene-addicted NSCLCs by induction of antibody-dependent cellular cytotoxicity (ADCC) and simultaneous inhibition of multiple signalling pathways (66).

HER3 is typically overexpressed on *EGFR*-mutated NSCLC (67) and patritumab deruxtecan (HER3-DXd) is an ADC against HER3. In a phase I study, ORR was 39% and median PFS was 8.2 months among 57 patients who had prior EGFR TKI and platinum-based chemotherapy and received HER3-DXd (68). The HERTHENA-Lung02

is a phase III study (NCT05338970) comparing HER3-DXd with platinum-based chemotherapy for patients with *EGFR*-mutated NSCLC failing osimertinib.

ALK rearrangement

Second and third generation ALK TKIs (namely ceritinib, alectinib, brigatinib, ensartinib, lorlatinib) have largely supplanted crizotinib for treatment-naïve, advanced *ALK*-rearranged NSCLC as all of them demonstrated superior PFS comparing with crizotinib in the upfront setting, except that ceritinib was compared with chemotherapy. (*Table 3*) (44-46,48-50,69). Although cross-trial comparison suggested that lorlatinib offered more durable disease control compared to the second generation ALK TKIs (3-year PFS 63% with lorlatinib, 45% with alectinib and 43% with brigatinib) (47,48,70), the optimal first-line treatment is still an open debate as lorlatinib usually remains effective after second generation ALK TKI failure (71).

Resistant *ALK* mutations most often occur in the gatekeeper region (e.g., L1196M and G1269A) or the solvent front region (e.g., G1202R) after first and second generation ALK TKI treatment (72). Serial ALK TKI treatment potentially predisposes to multiple resistant kinase mutations and lorlatinib resistance (73). Fourth generation ALK TKIs like TPX-0131 are designed to bind precisely to the adenine binding site of ATP to avoid clashing with the solvent front, hinge or gatekeeper area, and thus may overcome double- or triple-mutant resistant kinase mutations (74). TPX-0131 and NVL-655 are now being evaluated in phase I clinical studies which involve patients who have failed multiple lines of ALK TKI including lorlatinib (NCT04849273, NCT05384626).

ROS1 rearrangement

Crizotinib and entrectinib are approved therapies for *ROS1*-rearranged NSCLC. PROFILE 1001 was a single arm phase II study in which 50 patients with *ROS1*-rearranged NSCLC received crizotinib. Crizotinib achieved an ORR of 72% and a median PFS of 19.2 months (75). In the integrated analysis of three entrectinib studies (ALKA-372-001, STARTRK-1, and STARTRK-2), entrectinib achieved a similar ORR of 77% and a median PFS of 19.0 months (76). Entrectinib may be preferred in patients with brain metastases in view of its excellent intracranial activity (intracranial ORR 52.2%) (77). Besides crizotinib and entrectinib, ceritinib and lorlatinib are also both active in *ROS1*-rearranged NSCLC but are not FDA approved (78,79). $ROS1^{G2032R}$ solvent-front mutation is the most common resistance mechanism following crizotinib progression and confers resistance to all commercially available ROS1 inhibitors (80). Interim data of the TRIDENT-1 phase I/II study showed that repotrectinib (TPX-005), a next generation ROS1/TRK inhibitor, was active against ROS1 TKI-naïve and pretreated patients (81). Enrollment of this study is now ongoing (NCT03093116).

MET exon 14 skipping

Three highly selective type IB MET inhibitors, namely capmatinib, tepotinib, and savolitinib, were proven highly efficacious in patients with advanced *MET* exon 14 skipping positive (*MET*ex14) NSCLC. In GEOMETRY mono-1, treatment naïve patients with advanced *MET*ex14 NSCLC achieved an ORR of 68% and median PFS of 12.4 months with capmatinib. In the pretreated cohort, ORR was 41% and median PFS was 5.4 months (82,83). In the VISION study, 152 patients with NSCLC harbouring *MET*ex14, either detected by tissue or liquid biopsy, received tepotinib. Response rates were similar at 50% either in the tissue-biopsy or liquid-biopsy group, regardless of number of lines of previous treatment (84). Both drugs exhibited intracranial antitumour efficacy (84,85). Savolitinib was evaluated in 70 patients with pretreated *MET*ex14 NSCLC in China. Notably, 25 patients (36%) had pulmonary sarcomatoid carcinoma (PSC), which was underrepresented in the GEOMETRY mono-1 and the VISION study (<8% of patients had PSC). ORR in the intention-to-treat population and PSC subgroup were 49% and 40% respectively (86). Peripheral oedema is the major toxicity from MET inhibitors. Currently, capmatinib and tepotinib are FDA approved and savolitinib is approved in China for advanced *MET*ex14 NSCLC. Multiple treatment strategies targeting *MET*-dysregulated NSCLC, such as type II MET inhibitor (e.g., merestinib, NCT02920996), MET-based ADC (e.g., telisotuzumab vedotin, NCT03539536) and bispecific antibody (e.g., amivantamab, NCT02609776), are under study.

RET rearrangement

Recently, two selective RET inhibitors, demonstrated high efficacy in *RET* rearranged NSCLC and received FDA approvals for this treatment indication. Selpercatinib was tested in 144 patients with *RET*-rearranged NSCLC

in the LIBRETTO-001 multicentre single arm phase II study. In the treatment-naïve cohort, ORR was 85% and median PFS was not reached at data cutoff. In the platinum pretreated cohort, ORR was 64% and median PFS was 16.5 months (87). The ARROW study evaluated 121 patients with *RET*-rearranged NSCLC who received pralsetinib. ORR was 70% in the treatment naïve cohort and 61% in the pretreated cohort (88). Grade 3 and 4 toxicities due to RET inhibitors were rare and mainly included hypertension, deranged liver function, and cytopenia. The LIBRETTO-431 (NCT04194944) and ACCELERET (NCT04222972) are comparing selpercatinib and pralsetinib respectively, with platinum-based chemotherapy with or without pembrolizumab in patients with treatment-naïve advanced *RET*-rearranged NSCLC. Novel RET inhibitors (e.g., TPX-0046, NCT04161391; BOS172738, NCT03780517) designed to overcome acquired *RET* resistant mutations are now evaluated in phase I/II clinical trials (89,90).

BRAF V600E mutation

The combination of dabrafenib and trametinib is FDA approved for the treatment of advanced, *BRAF* V600E mutated NSCLC. Clinical efficacy achieved by the BRAF and MEK inhibitor combination (ORR 64% for both untreated and treatment naïve patients, median PFS 14.6 months for untreated cohort and 8.6 months for pretreated cohort) was considerably higher than BRAF inhibitor monotherapy (ORR about 40% and median PFS about 5–6 months) (91-93). Pyrexia is a specific and common (up to 50%) side effect from the drug combination which is usually ameliorated by antipyretics and dose adjustment.

NTRK rearrangement

Two TRK inhibitors, larotrectinib and entrectinib, received FDA approval as tumor agnostic therapies for patients with tumours harbouring *NTRK* fusions. In an updated integrated analysis of three phase I/II clinical trials which evaluated larotrectinib in 159 patients with *NTRK* fusion-positive solid tumours, ORR was 79% and median PFS was 25.8 months (94). Another integrated analysis of three phase I/II clinical trials analysed the clinical efficacy of entrectinib in 121 patients with *NTRK* fusion-positive tumours. The ORR was 61% and the median PFS was 13.8 months (95). Both larotrectinib and entrectinib showed high efficacy across a wide range of tumour types including NSCLC. TRK inhibitors are associated with specific on-target side events like cognitive impairment, dizziness, weight gain and drug withdrawal pain but drug discontinuation due to treatment-related adverse events is rare (<10%). In a small-scale study of 18 patients who progressed on first generation TRK inhibitors (larotrectinib or entrectinib), a resistant solvent front mutation was identified in 13 of them (96). Preclinical data showed that next generation TRK inhibitors such as taletrectinib, repotrectinib, and selirectinib, were effective against *NTRK* fusion positive tumours with secondary resistant *NTRK* mutations (81,97,98).

KRAS G12C mutation

KRAS was considered undruggable in the past due to the absence of an identifiable drug binding pocket on KRAS protein and its strong affinity to ATP rendering design of KRAS inhibitors inherently difficult (99). In 2013, the Shokat lab identified a small pocket adjacent to the switch-II region that was only present in GDP-bound, G12C mutant KRAS protein. The research team designed a small, KRAS G12C allele-specific molecule (ARS-1620) that could bind to this pocket and lock the KRAS protein in its inactive, GDP-bound state (100). Non-cancer cells that do not carry the *KRAS* G12C mutation could be spared from the toxicities, resulting in a much wider therapeutic index. Further refinement in drug structure designs have led to development of molecules with enhanced potency that are tested in clinic today.

Sotorasib (AMG510) was the first KRAS G12C inhibitor adopted in clinic setting. In CodeBreak 100 study, the drug was evaluated in 126 patients with pretreated *KRAS* G12C mutated NSCLC. The ORR was 37% and the median PFS was 6.8 months (101). Recently, the results of the phase III CodeBreak 200 trial were published. Sotorasib achieved superior PFS and ORR compared to docetaxel in patients who progressed after prior platinum-based chemotherapy and immune checkpoint inhibitor (102). Another KRAS G12C inhibitor, adagrasib (MRTX849), achieved treatment response rate of 43% and median PFS 6.5 months in the KRYSTAL-1 phase I-II study enrolling 116 patients (103). A number of KRAS G12C inhibitors, such as JDQ443, JAB-21822, and GDC-6036, are under clinical investigation (NCT05132075, NCT05276726, NCT04449874).

A heterogenous spectrum of resistance mechanisms have been identified in the setting of KRAS G12C inhibitor resistance, of which secondary *KRAS* mutations

or alterations in RTK-RAS signalling pathway are most prevalent (104,105). These data supported the approach of combining a KRAS G12C inhibitor with an RTK or SHP2 inhibitor in order to achieved more sustained RAS inhibition (NCT04330664, NCT04185883).

Targeting *KRAS* mutants other than G12C is more challenging given the lack of a drug binding pocket and even higher affinity to GTP. Nonetheless, preclinical data on KRAS G12D, KRAS G12V, and pan-KRAS inhibitors is emerging (106-110).

EGFR exon 20 insertion

EGFR exon 20 insertion (*EGFR*ex20ins) is well known to be EGFR TKI resistant due to its unique steric configuration. Recently, two drugs were approved by the FDA for treatment of advanced *EGFR*ex20ins NSCLC in the second line setting. Mobocertinib is an oral TKI designed specifically targeting *EGFR*ex20ins. The drug achieved an ORR of 28% and median PFS of 7.3 months in platinum-pretreated patients with advanced *EGFR*ex20ins NSCLC (111). Amivantamab is a bispecific EGFR-cMET antibody achieving a tumour response rate of 40% and median PFS of 8.3 months in 81 patients in the CHRYSALIS study (112).

HER2 mutation

Studies in the past targeting *HER2* mutation have yielded disappointing results. Various classes of anti-HER2 agents, including monoclonal antibodies, TKIs, and ADCs, have been investigated in *HER2*-mutated NSCLC. Recently, a few agents have demonstrated signals of antitumour activity (113-116). Among all anti-HER2 targeted therapies, trastuzumab deruxtecan (T-DXd) has shown the best promise. Compared to trastuzumab emtansine (T-DM1), T-DXd has a different cytotoxic payload and an enhanced linker-payload system enabling a higher drug-to-antibody ratio (1 to 8 for T-DXd compared to 1 to 4 for T-DM1) while maintaining high stability in plasma (117). Recently, the results of DESTINY-Lung01 trial were published. Total of 91 patients with *HER2*-mutated NSCLC were enrolled into the study. T-DXd achieved an ORR of 55%, DCR of 92% and median PFS of 8.2 months. Interstitial lung disease is a specific adverse event of T-DXd that occurred in a quarter of patients in this study (118). In August 2022, the FDA granted accelerated approval to T-DXd for patients with advanced HER2-mutated NSCLC failing first-line therapy. The upcoming DESTINY-Lung04 study will evaluate T-DXd versus standard of care in patients with untreated, advanced NSCLC harbouring a *HER2* mutation (NCT05048797).

NRG1 rearrangement

NRG1-rearrangement represents a rare but targetable oncogene in NSCLC (0.2%) and causes cancer by inducing ErbB2-ErbB3 dimerization. Zenocutuzumab, a bispecific HER2/HER3 antibody, and seribantumab, an anti-HER3 monoclonal antibody, showed encouraging signal in targeting *NRG1*-rearranged solid tumours including NSCLC (119-121). Both drugs are now being studied in phase II studies (NCT02912949, NCT04383210).

Antibody-drug-conjugates under development

TROP2 is ubiquitously expressed on lung cancer cells and thus a favourable target for development of ADC (120). Sacituzumab govitecan is a TROP-2 ADC connected to an irinotecan derivative payload SN-38. In a single arm cohort enrolling 54 heavily pretreated patients, ORR was 17% (122). Datopotamab deruxtecan (Dato-DXd) is another TROP-2 ADC using deruxtecan as the cytotoxic payload. In the NSCLC cohort of the TROPION-PanTumor01 Phase I study, ORR was 24%. Interstitial lung disease was present in 11% of patients (123). Dato-DXd was also active in patients with actionable genetic alterations (124). Tusamitamab ravtansine, an anti-CEACAM5 ADC, has shown antitumour efficacy in NSCLC. Tumour response rate was 20% in a heavily pretreated population with CEACAM5 highly expressed NSCLC (125). These drugs are now compared with docetaxel in the platinum-refractory setting (NCT04656652, NCT05089734, NCT04154956), and combinations of TROP-2 ADC with immunotherapy are also explored (NCT04526691, NCT04612751, NCT05186974).

Targeted therapy: future direction

Advances in structural bioinformatics and computational biology have led to drug discoveries that target "undruggable" alterations such as *KRAS* and *EGFRex20ins*. Consequently, targeted therapies are no longer limited to TKIs and monoclonal antibodies, but also comprise allosteric inhibitors, ADCs and bispecific antibodies. Increasing adoption of high throughput genomic sequencing as well as liquid biopsy testing has facilitated detection of rare genetic alterations and depiction of drug resistance

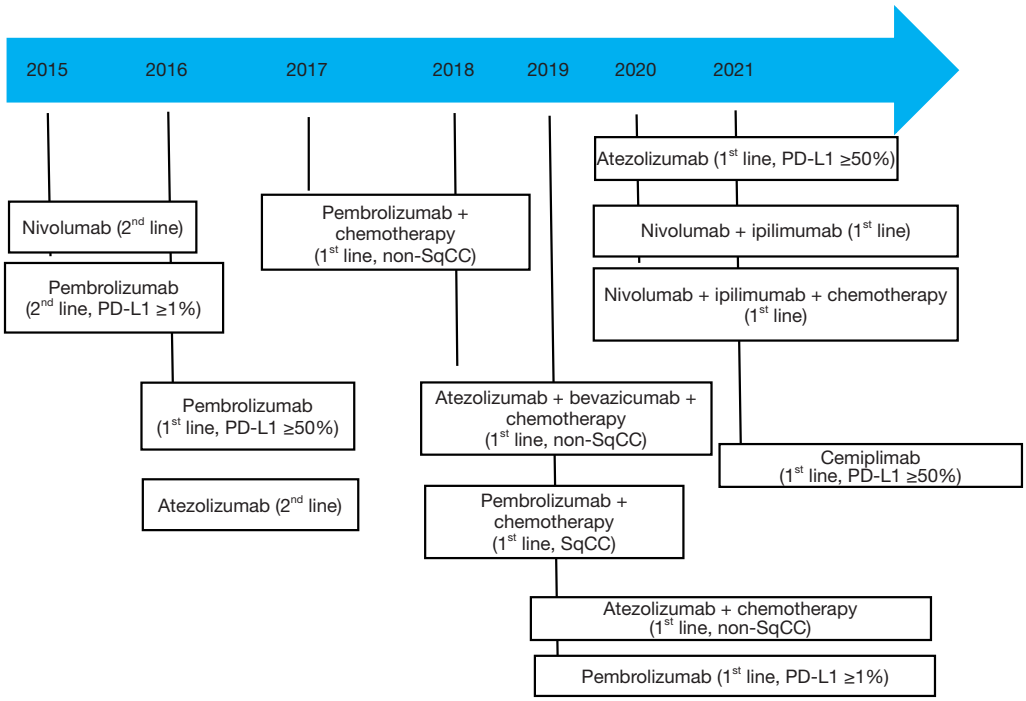

Figure 2 Timeline of FDA approval of immunotherapy in metastatic NSCLC. PD-L1, programme death-ligand 1; NSCLC, non-small cell lung cancer; non-SqCC, non-squamous.

mechanisms. Ongoing research focuses on characterization of TKI resistance mechanisms and development of novel therapeutic approaches targeting actionable resistance alterations. As a result, molecular profiling is not only essential at the time of diagnosis, but it may be clinically relevant to track the evolution and genomic changes of the tumour during the treatment course in order to establish a personalized therapeutic strategy.

Immunotherapy in metastatic NSCLC

PD-L1 blockade

Immune checkpoint inhibitor (ICI), notably anti-PD-L1/PD-1 antibody, is the cornerstone of immunotherapy for multiple cancer types including NSCLC. PD-1/PD-L1 binding leads to intratumoral T-cell exhaustion thus blocking this interaction may reactivate exhausted T-cells for cancer cell killing. PD-(L)1 blockade is now considered standard of care for patients with advanced NSCLC without actionable oncogenic alterations. At present, multiple anti-PD-(L)1 agents have been approved for metastatic NSCLC, either as monotherapy or in combination with other drugs (*Figure 2*). Treatment efficacy of anti-PD-(L)1 directly correlates with PD-L1 expression on tumour cells. For patients with treatment naïve, *EGFR/ALK* negative NSCLC with PD-L1 tumour proportion score (TPS) ≥50%, first-line anti-PD-(L)1 monotherapy was superior to chemotherapy in terms of PFS and OS (126-128) (*Table 4*) In the KEYNOTE-024 study, five-year overall survival was 31% for patients assigned to the pembrolizumab arm (129). Pembrolizumab monotherapy is approved but generally not recommended for patients with NSCLC with PD-L1 TPS 1–49%, as subgroup analysis showed no survival benefit over chemotherapy (127,130).

Addition of pembrolizumab to chemotherapy improved PFS and OS compared to chemotherapy alone regardless of PD-L1 expression and histology, and this regime has been adopted as the standard first-line treatment regime for advanced NSCLC without actionable alterations in multiple countries (131,133). Other studies testing immunochemotherapy combination with atezolizumab, sintilimab, tislelizumab, camrelizumab, or sugemalimab in addition to chemotherapy also consistently showed PFS improvement over chemotherapy alone (134-144) (*Table 4*). All of the studies above excluded patients with *EGFR* or

Table 4 Key randomized immunotherapy trials in treatment naïve, EGFR/ALK-ve, NSCLC

Study name	Intervention	Comparator	Key inclusion criteria	Median PFS, months, HR (95% CI)	Median OS, months, HR (95% CI)	Ref
Anti-PD-(L)1 single agent						
KEYNOTE-024	Pembrolizumab	Platinum based chemotherapy	NSCLC PD-L1 TPS ≥50%	10.3 *vs.* 6.0, HR 0.50 (0.37 to 0.68)	30.0 *vs.* 14.2, HR 0.63 (0.47 to 0.86)	(126,129)
Impower110	Atezolizumab	Platinum based chemotherapy	NSCLC PD-L1 ≥50% of tumour cells or ≥10% of tumour-infiltrating immune cells	8.1 *vs.* 5.0, HR 0.63 (0.45 to 0.88)	20.2 *vs.* 13.1, HR 0.59 (0.40 to 0.89)	(127)
EMPOWER-Lung 1	Cemiplimab	Platinum based chemotherapy	NSCLC PD-L1 TPS ≥50%	8.2 *vs.* 5.7, HR 0.54 (0.43 to 0.68)	NR *vs.* 14.2, HR 0.57 (0.42 to 0.77)	(128)
KEYNOTE-042	Pembrolizumab	Platinum based chemotherapy	NSCLC PD-L1 TPS ≥1%	5.4 *vs.* 6.5, HR 1.07 (0.94 to 1.21)	16.7 *vs.* 12.1, HR 0.81 (0.71 to 0.93)	(130)
Anti-PD-(L)1 plus chemotherapy combination						
KEYNOTE-189	Pembrolizumab-platinum-pemetrexed	Platinum plus pemetrexed	Non squamous, any PD-L1 TPS	9.0 *vs.* 4.9, HR 0.48 (0.40 to 0.58)	22.0 *vs.* 10.7, HR 0.56 (0.45 to 0.70)	(131,132)
KEYNOTE-407	Pembrolizumab-platinum based chemotherapy	Platinum based chemotherapy	Squamous, any PD-L1 TPS	6.4 *vs.* 4.8, HR 0.56 (0.56 to 0.70)	15.9 *vs.* 11.3, HR 0.64 (0.49 to 0.85)	(133)
IMpower150	Atezolizumab-bevacizumab-carboplatin-paclitaxel	Bevacizumab-carboplatin-paclitaxel	Non-squamous, any PD-L1 TPS	8.3 *vs.* 6.8, HR 0.62 (0.52 to 0.75)	19.2 *vs.* 14.7, HR 0.78 (0.64 to 0.96)	(134)
IMpower132	Atezolizumab-platinum-pemetrexed	Platinum plus pemetrexed	Non squamous, any PD-L1 TPS	7.6 *vs.* 5.2, HR 0.60 (0.49 to 0.72)	17.5 *vs.* 13.6, HR 0.86 (0.71 to 1.06)	(135)
IMpower130	Atezolizumab-carboplatin-nab-paclitaxel	Carboplatin plus nab-paclitaxel	Non squamous, any PD-L1 TPS	7.0 *vs.* 5.5, HR 0.64 (0.54 to 0.77)	18.6 *vs.* 13.9, HR 0.79 (0.64 to 0.98)	(136)
IMpower131	Atezolizumab-carboplatin-nab-paclitaxel	Carboplatin plus nab-paclitaxel	Squamous, any PD-L1 TPS	6.3 *vs.* 5.6, HR 0.71 (0.60 to 0.85)	14.2 *vs.* 13.5, HR 0.88 (0.73 to 1.05)	(137)
ORIENT-11	Sintilimab-platinum-pemetrexed	Platinum plus pemetrexed	Non squamous, any PD-L1 TPS	8.9 *vs.* 5.0, HR 0.482 (0.362 to 0.643)	NR *vs.* NR, HR 0.609 (0.400 to 0.926)	(138)
ORIENT-12	Sintilimab-platinum-gemcitabine	Platinum plus gemcitabine	Squamous, any PD-L1 TPS	5.1 *vs.* 4.9, HR 0.621 (0.473 to 0.815)	Not reached	(139)
RATIONALE 304	Tislezumab-platinum-pemetrexed	Platinum plus pemetrexed	Non squamous, any PD-L1 TPS	9.7 *vs.* 7.6, HR 0.645 (0.462 to 0.902)	Not reached	(140)
RATIONALE 307	Tislezumab-carboplatin-paclitaxel (Arm A)	Carboplatin-paclitaxel (Arm C)	Squamous, any PD-L1 TPS	7.6 *vs.* 5.5, HR 0.524 (0.370 to 0.742)	Not reached	(141)
	Tislezumab-carboplatin-nab-paclitaxel (Arm B)			7.6 *vs.* 5.5, HR 0.478 (0.336 to 0.679)	Not reached	
CameL	Camrelizumab-carboplatin-pemetrexed	Carboplatin-pemetrexed	Non-squamous, any PD-L1 TPS	11.3 *vs.* 8.3, HR 0.60 (0.45 to 0/79)	NR *vs.* 20.9, HR 0.73 (0.53 to 1.02)	(142)
CameL-Sq	Camrelizumab-carboplatin-paclitaxel	Carboplatin-paclitaxel	Squamous, any PD-L1 TPS	8.5 *vs.* 4.9, HR 0.37 (0.29 to 0.47)	NR *vs.* 14.5, HR 0.55 (0.40 to 0.75)	(143)
GEMSTONE-302	Sugemalimab-platinum based chemotherapy	Platinum based chemotherapy	NSCLC, any PD-L1 TPS	9.0 *vs.* 4.9, HR 0.48 (0.39 to 0.60)	22.8 *vs.* 17.7, HR 0.67 (0.50 to 0.90)	(144)

Table 4 *(contiued)*

Table 4 *(contiued)*

Study name	Intervention	Comparator	Key inclusion criteria	Median PFS, months, HR (95% CI)	Median OS, months, HR (95% CI)	Ref
Anti-PD-(L)1 plus anti-CTLA4 +/- chemotherapy combination						
CheckMate 227	Nivolumab plus Ipilimumab	Platinum based chemotherapy	NSCLC, PD-L1 TPS ≥1%	5.1 *vs.* 5.6, HR 0.82 (0.69 to 0.97)	17.1 *vs.* 14.9, HR 0.79 (0.65 to 0.96)	(145)
			PD-L1 TPS <1%	5.1 *vs.* 4.7, HR 0.75 (o.59 to 0.96)	17.2 *vs.* 12.2, HR 0.62 (0.48 to 0.78)	
CheckMate 9LA	Nivolumab, ipilimumab, platinum based chemotherapy	Platinum based chemotherapy	NSCLC, any PD-L1 TPS	6.7 *vs.* 5.0, HR 0.68 (0.57 to 0.82)	15.6 *vs.* 10.9, HR 0.66 (0.55 to 0.80)	(146)
MYSTIC	Durvalumab plus tremelimumab	Platinum based chemotherapy	NSCLC, PD-L1 TPS ≥25%	3.9 *vs.* 5.4, HR 1.05 (0.72 to 1.53)	11.9 *vs.* 12.9, HR 0.85 (0.61 to 1.17)	(147)
NEPTUNE	Durvalumab plus tremelimumab	Platinum based chemotherapy	NSCLC with bTMB ≥20 mut/Mb	4.2 *vs.* 5.1, HR 0.77 (0.51 to 1.15)	11.7 *vs.* 9.1, HR 0.71 (0.49 to 1.05)	(148)

NSCLC, non-small cell lung cancer; HR, hazard ratio; NR, not reached; OS, overall survival; PD-L1, programme death-ligand 1; PFS, progression-free survival; Ref, reference; TPS, tumor proportion score; bTMB, blood tumour mutational burden.

ALK alterations. CheckMate 722 (NCT02864251) and KEYNOTE789 (NCT03515837) are phase III studies investigating the combination of anti-PD-(L)1 plus chemotherapy versus chemotherapy in advanced *EGFR*-mutated *NSCLC* NSCLC failing TKI. Results are eagerly awaited.

Despite the promise of anti-PD-(L)1 blockade, only a minority of patients experience durable benefit. Complex interplay between the immune system, tumour cells and tumour microenvironment (TME) are implied in the setting of immunotherapy resistance. ICI resistance can be broadly classified into tumour intrinsic and tumour extrinsic. Tumour intrinsic mechanisms include low tumour antigen production, defective antigen presentation or expression of co-inhibitory signals. Tumour extrinsic mechanisms include failure in T cell activation or infiltration into tumour, or intratumoral T cell dysfunction, either due to defects in host immune system or an immunosuppressive TME. To date, the landscape of ICI resistance is still poorly understood. Combinational strategies designed to overcome these resistance mechanisms are now investigated in clinical trials.

Immune checkpoints: *CTLA4*, *TIGIT, and others*

Cytotoxic T lymphocyte antigen 4 (CTLA4) is an immune checkpoint mechanistically distinct from PD-L1. It interferes with B7-CD28 binding and prevents T cell priming inside lymph nodes. It is also highly expressed by regulatory T (Treg) cells, thus blocking CTLA4 may both enhance T cell activation and downregulate Treg cells. CheckMate-227, MYSTIC and NEPTUNE study evaluated the anti-PD-L1/anti-CTLA4 combination without chemotherapy versus chemotherapy alone for treatment-naïve, EGFR/ALK negative, advanced NSCLC (*Table 4*). In the CheckMate-227 study, superior OS was achieved with nivolumab plus ipilimumab compared to chemotherapy, regardless of PD-L1 expression (146). Contrarily, both MYSTIC and NEPTUNE studies failed to achieve their primary endpoints—OS was not superior with dual immunotherapy in a biomarker-specified population (147,149). Both CheckMate-9LA and POSEIDON study showed that the four-drug combination of anti-PD-(L)1, anti-CTLA4 and chemotherapy was superior to chemotherapy alone in terms of PFS and OS, establishing the combination of dual immunotherapy plus chemotherapy as a valid first-line treatment option (146,150). Incidence of immune-related adverse events and rate of immunotherapy discontinuation was higher with dual immunotherapy compared to anti-PD-(L)1 monotherapy (145,149).

Prospective evidence is lacking in identifying patients who may benefit more from dual immunotherapy over anti-PD-(L)1 monotherapy. KEYNOTE-598 randomized patients with PD-L1 ≥50%, treatment-naïve advanced NSCLC to pembrolizumab single agent versus pembrolizumab plus ipilimumab. No PFS or OS

improvement but only increased toxicities were observed in the dual immunotherapy arm (151). Based on this study, dual PD-(L)1 and CTLA blockade is not recommended for PD-L1 ≥50% NSCLCs.

Aside PD-L1 and CTLA4, multiple immune checkpoints are being evaluated as anticancer therapeutic targets. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a co-inhibitory immune receptor expressed on T cells. Preclinical data showed that dual TIGIT/PD-1 blockade enhanced antitumour immune response (152). The phase II CITYSCAPE trial randomly assigned 135 patients with treatment naïve, PD-L1 ≥1% to atezolizumab plus tiragolumab and atezolizumab alone. Patients in the atezolizumab plus tiragolumab arm achieved higher ORR (ORR 37% versus 21%), although the benefit was mainly driven by the PD-L1 ≥50% subgroup (ORR in PD-L1 ≥50% 69% versus 24%) (153). However, Roche recently reported that the phase III SKYSCRAPER-01 study, assessing tiragulomab plus atezolizumab versus atezolizumab alone for patients with PD-L1 high, *EGFR/ALK* negative, treatment naïve, advanced NSCLC, did not meet the co-primary end point of PFS (154). Apart from TIGIT, antibodies blocking other co-inhibitory immune checkpoints such as LAG3, TIM3 and VISTA and activating co-stimulatory receptors such as OX-40, ICOS, CD137 and GITR, are now studied in early-phase trials, either in monotherapy or in combination with anti-PD-(L)1 antibody (*Table 5*).

Combination with anti-VEGF

Abnormal vasculature is a hallmark of cancer. Anti-angiogenesis agents can potentially modulate an immunosuppressive TME and enhance trafficking as well as tumour infiltration of immune cells (155).

Despite the proven synergism between anti-PD-(L)1 and anti-vascular endothelial growth factor (VEGF) in multiple cancer types, such evidence is more controversial in NSCLC (156-158). The IMpower150 study was a positive trial showing improved PFS and OS in patients who received atezolizumab-bevacizumab-chemotherapy compared to bevacizumab-chemotherapy, but this study did not directly answer the question whether bevacizumab had added value on top of PD-L1 blockade (134). LEAP-007 randomized patients with untreated, *EGFR/ALK* negative, PD-L1 TPS ≥1% advanced NSCLC to pembrolizumab versus pembrolizumab plus lenvatinib. This was a negative study (OS 14.1 versus 16.4 months, HR 1.10, OS numerically lower in pembrolizumab/lenvatinib arm) (159). However, Reckamp *et al.* recently reported in a phase II study in which patients who were previously treated with ICI and platinum-based chemotherapy, OS was significantly improved with pembrolizumab plus ramucirumab compared to chemotherapy of physician's choice [OS 14.5 versus 11.6 months, HR 0.69 (80% CI: 0.51–0.92)] (160). This suggested that antiangiogenic agents did resensitize tumours to ICI in a certain subset of patients. Ongoing clinical studies with biomarker analyses will further define patients who may potentially benefit from antiangiogenic agents (*Table 5*).

Cancer vaccines

Low tumour neoantigen expression and defective antigen presentation are two fundamental reasons of impaired T cell activation and ICI failure. Cancer vaccine primarily works by enhancing antigen-specific T cell antitumour responses. Most cancer vaccines tested in lung cancer clinical trials utilized tumour-associated antigens (TAAs), such as melanoma-associated antigen-A3 (MAGE-A3) and mucin 1 (MUC-1), self-antigens that are commonly overexpressed but not uniquely expressed on tumour cells. Two phase III studies, MAGRIT and START, evaluated MAGE-A3 vaccine and MUG1 antigen vaccine versus placebo respectively in the adjuvant setting. Both studies failed to report survival benefit with the study treatment (161,162).

Following the disappointing results of single-antigen vaccination, clinical research now focuses on multiple-antigen vaccination and personalized antigen vaccination. In the first part of the phase III ATALANTE-1 randomised trial, OSE-2101, a HLA-A2 restricted neoepitope vaccine targeting five TAAs (CEA, HER2, MAGE2, MAGE3, and P53) expressed on lung cancer cells, achieved superior OS over standard-of-care second-line chemotherapy in patients failing platinum-based chemotherapy and anti-PD-(L)1 treatment (163). Part 2 is now ongoing and will enroll 363 participants with OS as the primary endpoint (NCT02654587). Personalized antigen vaccination is constructed by whole exome and RNA sequencing of the tumour and identification of personalized immunogenic neoepitopes based on bioinformatic algorithms (164). In a phase Ib study, response rate was 39% with no extra safety signals reported in 18 patients in the NSCLC cohort who received NEO-PV-01 (a personalized neoantigen vaccine) concurrently with nivolumab (165). Multiple studies on personalized cancer vaccine are now ongoing either as monotherapy or given in combination with ICIs (*Table 5*).

Table 5 Clinical Trials on novel targets to overcome ICI resistance in advanced NSCLC[†]

Target	Treatment strategy	Setting	Phase	Study name (NCT identified)
Inhibitory immune checkpoints				
TIGIT	Atezolizumab with or without tiragolumab	Treatment naïve, high PD-L1 expression	III	SKYSCRAPER-01 (NCT04294810)
	Pembrolizumab with or without vibostolimab	Treatment naïve, PD-L1 TPS ≥1%	III	KEYVIBE-003 (NCT04738487)
	Pembrolizumab plus chemotherapy with or without vibostolimab	Treatment naive	III	KEYVIBE-007 (NCT05226598)
	MK-7684A (pembrolizumab/vibostolimab coformulation) with or without docetaxel (*vs.* docetaxel)	Prior ICI	II	KEYVIBE-002 (NCT04725188)
	Pembrolizumab plus vibostolimab plus platinum based chemotherapy	ICI naive	I	KEYVIBE-001 (NCT02964013)
	Tislelizumab plus ociperilimab versus pembrolizumab or tislelizumab	Treatment naïve, PD-L1 TPS ≥50%	III	(NCT04746924)
	Tislelizumab plus chemotherapy with or without ociperlimab	Treatment naive	II	(NCT05014815)
	Zimberelimab (anti-PD-1) plus domvanalimab (anti-TIGIT) plus etrumadenant (A2R antagonist)	Prior ICI, PD-L1 TPS ≥1%	II	(NCT04791839)
	Zimberelimab or zimberelimab plus domvanalimab or zimberelimab plus domvanalimab plus etrumadenant	Treatment naïve, PD-L1 TPS ≥50%	II	(NCT04262856)
	Zimberelimab with or without domvanalimab, versus chemotherapy	Treatment naïve, PD-L1 TPS ≥1%	III	(NCT04736173)
	AZD2936 (anti-TIGIT/anti-PD-1 bispecific antibody)	Prior ICI	I/II	(NCT04995523)
	HLX301 (anti-TIGIT/anti-PD-1 bispecific antibody)	Pretreated	I/II	(NCT05102214)
LAG-3	XmAb22841 with or without pembrolizumab	Pretreated	I	(NCT03849469)
	RO7247669 monotherapy	Pretreated	I	(NCT04140500)
	Eftilagimoid alpha plus pembrolizumab	Treatment naïve/prior ICI	II	(NCT03625323)
	LAG525 with or without spartalizumab	Pretreated	I/II	(NCT02460224)
TIM-3	TSR-022 alone, or plus nivolumab or TSR-042 or TSR-033 or chemotherapy, or a combination of three drugs	Pretreated	I	(NCT02817633)
	RO7121661 monotherapy	Pretreated	I	(NCT03708328)
	INCAGNO2390	Pretreated	I	(NCT03652077)
	BGB-A425 plus tislelizumab	Pretreated	I/II	(NCT03744468)
	AZD7789 (anti-PD-1/anti-TIM-3 bispecific antibody)	Prior ICI	I/II	(NCT04931654)
	MBG453 with or without spartalizumab	Pretreated	I/II	(NCT02608268)
S-15	NC318 monotherapy	Pretreated	I/II	(NCT03665285)
	NC318 plus pembrolizumab	Prior ICI	II	(NCT04699123)
VISTA	HMBD-002 with or without pembrolizumab	Pretreated	I	NCT05082610

Table 5 *(contiued)*

Table 5 *(contiued)*

Target	Treatment strategy	Setting	Phase	Study name (NCT identified)
Stimulatory signals				
OX-40	PF-04518600 with or without utomilumab	Prior ICI	I	(NCT02315066)
	INCAGN01949 plus nivolumab or ipilimumab or nivolumab-ipilimumab	Pretreated	I/II	(NCT03241173)
	SL-279252 (PD1-Fc-OX40L)	Pretreated	I	(NCT03894618)
	INBRX-106 with or without pembrolizumab	Pretreated	I	(NCT04198766)
CD40	APX005M plus nivolumab	ICI naïve and pretreated	I/II	(NCT03123783)
	CDX-1140, monotherapy, with CDX-301 (FLT3L), pembrolizumab or chemotherapy	Pretreated	I	(NCT03329950)
	SEA-CD40 with or without pembrolizumab	Pretreated	I	(NCT02376699)
	SEA-CD40 with pembrolizumab and platinum based chemotherapy	ICI naive	II	(NCT04993677)
ICOS	Vopratelimab plus ipilimumab	Prior ICI	II	(NCT03989362)
	Vopratelimab plus JTX-4014	Pretreated	II	(NCT04549025)
	GSK3359606 plus tremelimumab	Pretreated	I/II	(NCT03693612)
	GSK3359609 plus docetaxel	Pretreated	II	(NCT03739710)
	KY1044 with or without atezolizumab	Pretreated	I/II	(NCT03829501)
CD137	INBRX-105 with or without pembrolizumab	Prior ICI	I	(NCT03809624)
GITR	INCAGN01876 plus nivolumab or ipilimumab or nivolumab-ipilimumab	Pretreated	I/II	(NCT03126110)
VEGF				
	Pembrolizumab plus Lenvatinib or placebo	Untreated, PD-L1 TPS ≥1%	III	LEAP-007 (NCT03829332)
	Pembrolizumab plus platinum-pemetrexed plus lenvatinib or placebo	Untreated, non squamous	III	LEAP-006 (NCT03829319)
	Pembrolizumab plus Lenvatinib (versus docetaxel)	Prior ICI and chemo	III	LEAP-008 (NCT03976375)
	Nivolumab plus sitravatinib (versus docetaxel)	Prior ICI and chemo	III	SAPPHIRE (NCT03906071)
	Atezolizumab plus bevacizumab	Untreated, TMB ≥10	II	(NCT03836066)
	Atezolizumab plus bevacizumab (versus atezolizumab)	Untreated, PD-L1 TPS ≥1%	II	(NCT03896074)
	Atezolizumab plus platinum-based chemotherapy plus bevacizumab	Untreated	II	(NCT03713944)
	Atezolizumab plus platinum-based chemotherapy with or without bevacizumab	Untreated	II	(NCT03786692)
	Atezolizumab plus ramucirumab	Prior ICI	II	(NCT03689855)
	Pembrolizumab plus ramucirumab (versus SOC)	Prior ICI	II	(NCT03971474)
	Pembrolizumab plus ramucirumab plus docetaxel	Prior ICI and chemo	II	(NCT04340882)
	Nivolumab plus ramucirumab	Prior ICI	II	(NCT03527108)
	Nivolumab plus ipilimumab plus nintedanib	Treatment naïve and ICI pretreated	I/II	(NCT03377023)
	Pembrolizumab plus lenvatinib	Prior ICI	I/II	(NCT02501096)
	Avelumab plus axitinib	ICI naive	II	(NCT03472560)

Table 5 *(contiued)*

Table 5 *(contiued)*

Target	Treatment strategy	Setting	Phase	Study name (NCT identified)
Cancer vaccine				
	OSE2101 (*vs.* standard treatment)	Prior ICI and chemo	III	ATALANTE 1 (NCT02654587)
	RO7198457 with or without atezolizumab	ICI naïve and pretreated	I	(NCT03289962)
	Viagenpumatucel-L plus nivolumab or pembrolizumab plus pemetrexed	Prior ICI	I/II	(NCT02439450)
	NEO-PV-01 plus pembrolizumab plus platinum based chemotherapy	Untreated	I	(NCT03380871)
	GAd-PEV and MVA-PEV (personalized vaccine) with pembrolizumab	ICI naïve, PD-L1 TPS ≥50%	I	(NCT04990479)
	TG4010 (modified-human mucin 1-interleukin-2) vaccine with nivolumab	ICI naive	II	(NCT02823990)
Adoptive cellular therapy				
TIL	Autologous TILs plus nivolumab	ICI naive	I	(NCT03215810)
	LN-145	Prior ICI	II	(NCT04614103)
	ATL001 with or without pembrolizumab	Prior ICI	I/II	(NCT04032847)
	ITIL306	Prior ICI and chemo	I	(NCT05397093)
TCR T cells	Anti-NY-ESO-1 TCR T cells	Pretreated	I/II	(NCT05296564)
	NY-ESO-1/LAGE-1a TCR T cells with or without pembrolizumab	Pretreated	II	(NCT03709706)
	Gene-edited autologous neoTCR-T cells monotherapy, or in combination with nivolumab or interleukin-2	Pretreated	I	(NCT03970382)
CAR-T	LYL797 (ROR1-targeted CAR T-cell therapy)	Pretreated	I	(NCT05274451)
	CAR-TnMUC1	Prior ICI and chemo	I	(NCT94925216)
NK-cells	GAIA-102 (activated NK-like cells)	Pretreated	I/II	(NCT05207371)
Cytokine				
TGF-B	Bintrafusp alfa (versus pembrolizumab)	Untreated, PD-L1 TPS ≥50%	III	INTR@PID Lung 037 (NCT03631706)
	Docetaxel with or without bintrafusp alfa	Prior ICI and chemo	II	(NCT04396535)
	TEW-7197 with durvalumab	ICI naive	I/II	(NCT03732274)
IL-1B	Pembrolizumab plus platinum based chemotherapy plus canakinumab or placebo	Untreated	III	CANOPY-1 (NCT03631199)
	Docetaxel plus canakinumab or placebo	Prior ICI and chemo	III	CANOPY-2 (NCT03626545)
	Spartalizumab plus platinum based chemotherapy with or without canakinumab	Prior ICI	I	(NCT03064854)
IL-2	NKTR-214 plus nivolumab	ICI naïve and pretreated	I/II	(NCT02983045)
	THOR-707 with or without immune checkpoint inhibitor	ICI naïve and pretreated	I/II	(NCT04009681)
	Nemvaleukin alfa with or without pembrolizumab	ICI naïve and pretreated	I/II	(NCT02799095)
	STK-012 (pegylated engineered interleukin-2)	Pretreated	I	(NCT05098132)
IL-15	ALT-803 plus nivolumab	Prior ICI	I/II	(NCT02523469)
	ALT-803 plus immune checkpoint inhibitor	Prior ICI	II	(NCT03228667)

Table 5 *(contiued)*

Table 5 *(contiued)*

Target	Treatment strategy	Setting	Phase	Study name (NCT identified)
IL-12	Adenoviral-mediated interleukin (ADV/IL-12) gene therapy (intratumoral ADV/IL-12 injection) with atezolizumab	Prior ICI	I	(NCT04911166)
Other TME targets				
IDO	Pembrolizumab with or without epacadostat	Untreated, PD-L1 TPS ≥50%	II	KEYNOTE-654-05 (NCT03322540)
	Pembrolizumab plus platinum based chemotherapy with or without epacadostat	Untreated	II	KEYNOTE-715-06 (NCT03322566)
	Nivolumab plus ipilimumab plus epacadostat	Pretreated	I/II	ECHO-208 (NCT03347123)
HDAC	Pembrolizumab plus mocetinostat plus guadecitabine	Prior ICI	I	(NCT03220477)
	Nivolumab plus glesatinib, sitravatinib, or mocetinostat	Prior ICI	II	(NCT02954991)
	Nivolumab plus entinostat plus azacytidine	Prior chemo, ICI naïve or pretreated	II	(NCT01928576)
	Pembrolizumab plus vorinostat	ICI naïve and pretreated, PD-L1 TPS ≥1%	I/II	(NCT02638090)
	Abexinostat plus pembrolizumab	Pretreated	I	(NCT03590054)
Adenosine	Spartalizumab plus NIR178	Pretreated	II	(NCT03207867)
	Durvalumab plus AZD4635	Prior ICI	I	(NCT02740985)
	Etrumadenant plus zimberelimab	Pretreated	I	(NCT03629756)
CDK4/6	Pembrolizumab plus abemaciclib	ICI naïve and pretreated	Ib	(NCT02779751)
PARP	Maintenance pembrolizumab plus olaparib *vs.* pembrolizumab plus pemetrexed	Untreated, non-squamous maintenance	III	KEYLYNK-006 (NCT03976323)
	Maintenance pembrolizumab plus olaparib or placebo	Untreated, squamous, maintenance	III	KEYLYNK-008 (NCT03976362)
	Avelumab plus talazoparib	Prior ICI, STK11 mutation	II	(NCT04173507)
MEK	Pembrolizumab plus trametinib	Pretreated, KRAS mutant	I	(NCT03299088)
	Pembrolizumab plus trametinib	pretreated	I/II	(NCT03225664)
	Durvalumab plus tremelimumab plus selumetinib	pretreated	I/II	(NCT03581487)
	Pembrolizumab plus binimetinib	Untreated, PD-L1 TPS ≥50%	I	(NCT03991819)
	Atezolizumab plus cobimetinib	Prior ICI	II	(NCT03600701)
AXL	Pembrolizumab plus bemcentinib	ICI naïve and pretreated	II	(NCT03184571)

†, not intended to be exhaustive. NSCLC, non-small cell lung cancer; NCT, National Clinical Trial; ICI, immune checkpoint inhibitor; PD-L1, programme death-ligand 1; TPS, tumour progression score.

Adoptive cellular therapy

Given the vital role of T cell in antitumour immunity, adoptive cellular therapy (ACT) developed to date has mainly focused on T cell therapy, although other cellular therapies (e.g., NK cell, B cell, macrophage) have demonstrated therapeutic potentials as well. Similar to cancer vaccine, the objective of ACT is to generate tumour-specific, activated immune cells (166). Adoptive T cell therapy includes tumour-infiltrating lymphocyte (TIL) therapy, T-cell receptor (TCR)-engineered T cell therapy and chimeric antigen receptor T-cell (CAR-T) therapy. TILs are polyclonal T cells isolated from patient's tumour

tissue, expanded ex-vivo and reinfused into the patient after lymphodepletion. In a recent phase I trial, TIL therapy was administered with nivolumab in 20 patients with advanced NSCLC upon progression on anti-PD-(L)1 treatment. The study met the end point of safety. Objective response was noted in three out of thirteen evaluable patients including two with durable complete responses (167). In TCR-engineered T cell and CAR-T cell therapy, autologous T cells are isolated from peripheral circulation followed by *ex-vivo* transduction of a tumour-antigen specific TCR or CAR (166). Despite its tremendous success in treating haematological malignancies, CAR-T for solid tumour treatment proves to be challenging due to factors like poor tumour infiltration, immunosuppressive TME, and off-target toxicities (168). Innovative approaches have been evaluated to overcome these resistance mechanisms. For instance, gene-edited T cells may enhance both safety as well as antitumour efficacy. In a phase I first-in-human study, CRISPR-Cas9 PD-1-edited T cells were safely given to 12 patients with advanced NSCLC without severe toxicities (169). Combination of cellular therapy with other modalities of immunotherapy, such as PD-L1 blockade or cytokine therapy, may further potentiate the therapeutic efficacy of tumour-specific immune cells (170,171).

Targeting tumour microenvironment, cytokine, and gut microbiota

Cytokines are pivotal in modulating immune cell function and thus have been actively investigated in enhancing antitumour efficacy of immunotherapy. This concept is supported by the fact that a minority of patients with melanoma and renal cell carcinoma achieved durable responses with high dose interleukin-2 (IL-2) therapy (172,173). A phase I study showed that the combination of NKTR-214 (a prodrug of polyethylene glycol (PEG)-conjugated IL-2) and nivolumab was safe and efficacious (three out of five patients with NSCLC achieved RECIST response) in immunotherapy-naïve patients with various cancer types including NSCLC (174,175). A global dose escalation study for treatment-naïve lung cancer patients is ongoing (NCT03138889). Another phase I study evaluated the combination of nivolumab and ALT-803, a modified IL-15/IL-15Rα/IgG1 Fc complex in patients with anti-PD-L1 antibody refractory NSCLC (NCT02523469). Twenty-one patients received study treatment and ORR was 29% (176).

Canakinumab, an anti-IL-1B monoclonal antibody, has been studied in multiple phase II and III studies after a significant reduction in lung cancer incidence and mortality was observed in the large scale CANTOS study which investigated the role of IL-1B in atherosclerosis (177). However, both the phase III CANOPY-1 (pembrolizumab plus chemotherapy with or without canakinumab in untreated metastatic NSCLC, NCT03631199) and CANOPY-2 (docetaxel with or without canakinumab in pretreated NSCLC) studies failed to improve PFS and OS (178,179). CANOPY-A and CANOPY-N are ongoing studies evaluating the drug in the neoadjuvant and adjuvant setting in early staged disease (NCT03447769, NCT03968419).

A multitude of enzymatic pathways and cellular components are associated with an immunosuppressive TME. These molecules have been explored as therapeutic targets in hope to modulate the TME and enhance immune activity. Histone deacetylase (HDAC) alters gene expression via epigenetic regulation and HDAC inhibitors are found to promote pro-immune activity within the TME. Two phase II studies reported antitumour activity and acceptable safety profile of HDAC inhibitor and anti-PD-(L)1 combination in patients with PD-(L)1 resistant/refractory NSCLC (180,181). Further clinical studies are warranted to select patients who may benefit from this drug combination. Other targets of interest, including indoleamine 2,3-dioxygenase (IDO), RORγ, AXL, MEK, PARP and CD73, are now being studied in early phase clinical trials enrolling NSCLC patients (*Table 5*).

Lastly, gut microbiota has emerged as a potential immune mediator that may affect clinical response to ICI treatment. Preclinical studies showed that a favourable gut flora composition is predictive of ICI response and modulation of gut flora may reverse ICI resistance (182). This strategy is now tested in prospective trials for patients with ICI failure, mainly by introducing favourable gut flora via faecal microbial transplantation and ICI rechallenge.

Immunotherapy in advanced NSCLC: future direction

Although the adoption of PD-L1 blockade has marked a new milestone of NSCLC management, ICI resistance and lack of predictive biomarker remain two major challenges. While various resistance models have been proposed, ICI resistance in reality is likely multifactorial and methods for ascertaining ICI resistance mechanisms are currently lacking. Combinational immunotherapy approaches targeting different phases of antitumour immunity have shown encouraging signals. However, most of these approaches were not tested in a biomarker-based fashion,

which might explain the failure of some phase II/III trials despite favourable results seen in early phase studies. More translational research is required to identify predictive biomarkers of ICI response or resistance. Advances in diagnostic and analytic tools like multiomic analysis, single cell sequencing, and deep learning approaches, may offer further insight into the dynamic interaction between the host immune system, cancer cells and TME.

Strengths and limitations of this review

This review offers a succinct overview in the latest update in targeted therapy and immunotherapy for NSCLC management, identified resistance mechanisms, and current research direction to overcome treatment resistance and further improve treatment outcome. Owing to the breadth of the topic, some sections cannot be discussed in depth. While the authors agree that the advances in molecular diagnostics and biomarker research is also crucial for the successful development of novel therapeutics, this topic is beyond the scope of this review.

Conclusions

Deeper understanding of the molecular and immune biology of NSCLC has led to rapid development of targeted therapy and immunotherapy in this field. The indications of targeted therapy and immunotherapy have now extended to early staged NSCLC as randomized studies have confirmed that these agents reduce disease recurrence. Comprehensive genomic profiling at diagnosis of advanced disease maximizes the chance for patient to benefit from highly efficacious molecular therapies. At the time of treatment resistance, next generation molecular therapies and novel drug combinations tailored to specific resistance mechanisms may now be considered. Currently, only a minority of patients experience durable clinical benefit with immunotherapy and innovative strategies targeting various immune resistance mechanisms have yielded early promise. As the therapeutic landscape of NSCLC is becoming increasingly complex, identification of predictive and resistance biomarkers is key to success in future drug development. The importance of multiomic profiling and translational studies alongside clinical trials cannot be overemphasized.

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& Consulting, Taiho Pharmaceutical and Touch Independent Medical Education; he serves as the Advisory Board Member for AbbVie, Amgen, Berry Oncology, Boehringer Ingelheim Pharmaceuticals, C4 Therapeutics, CStone Pharmaceuticals, D3 Bio Ltd., Eisai, G1 Therapeutics Inc., Gritstone Oncology Inc., GeneDecode Co Ltd, Hutchmed, Incyte Corporation, IQVIA, Lilly, Lunit, Merck Sharp & Dohme, Novartis, Puma Biotechnology, Roche/Genentech, SFJ Pharmaceutical, Vertex Pharmaceuticals, Yuhan Corporation, ACEA Pharma, AstraZeneca, Blueprint Medicines Corporation, Bristol-Myers Squibb Company, Covidien LP, Curio Science, Daiichi Sankyo, Fishawack Facilitate, Gilead Sciences, Guardant Health, Hengrui Therapeutics, Ignyta, Inivata, Janssen, Loxo-Oncology, Merck Serono, Mirati Therapeutics, Origimed, Pfizer, Sanofi-Aventis R&D, Takeda and Virtus Medical Group; he serves as the Board of Directors (remunerated) for AstraZeneca PLC, Lunit USA, HutchMed and ACT Genomics-Sanomics Group; he has the leadership role (non-remunerated) in Chinese Society of Clinical Oncology (CSCO), Hong Kong Cancer Therapy Society (HKCTS), Asian Thoracic Oncology Research Group (ATORG), American Society of Clinical Oncology (ASCO), Chinese Lung Cancer Research Foundation Limited (CLCRF), Hong Kong Cancer Fund (HKCF) and International Association for the Study of Lung Cancer (IASLC). Besides, he holds equities in Aurora Tele-Oncology Ltd., HutchMed and ACT Genomics-Sanomics Group. The authors have no other conflicts of interest to declare.

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