THERAPEUTIC ADVANCES in
Medical Oncology

Review

Targeting the MET gene: unveiling therapeutic opportunities in immunotherapy within the tumor immune microenvironment of non-small cell lung cancer

Ther Adv Med Oncol

2024, Vol. 16: 1–20

DOI: 10.1177/17588359241290733

Lisha Ye*, Wenjing Wang*, Huihui Li, Yongling Ji, Xiuning Le and Xiaoling Xu

***Abstract*:** Non-small cell lung cancer (NSCLC) represents the most prevalent histological subtype of lung cancer. Within this disease, the MET gene emerges as a critical therapeutic target, exhibiting various forms of dysregulation. Although MET tyrosine kinase inhibitors, HGF/c-MET targeting antibodies, and antibody-drug conjugates constitute the primary treatment modalities for patients with MET-altered NSCLC, numerous questions remain regarding their optimal application. The advent of immunotherapy holds promise for enhancing therapeutic outcomes in patients with MET-altered NSCLC. MET mutations can reshape the tumor immune microenvironment of NSCLC by reducing tumor immunogenicity, inducing exhaustion in immune-activated cells, and promoting immune evasion, which are crucial for modulating treatment responses. Furthermore, we emphasize the promising synergy of immunotherapy with emerging treatments and the challenges and opportunities in refining these approaches to improve patient outcomes.

Keywords: antibody-drug conjugate, c-MET, immunotherapy, non-small cell lung cancer (NSCLC), tumor immune microenvironment (TIME)

Received: 13 July 2024; revised manuscript accepted: 25 September 2024.

Correspondences to:
Yongling Ji
Postgraduate Training Base Alliance, Wenzhou Medical University, Wenzhou 325035, Zhejiang, China

Department of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, No.1 Banshan East Road, Hangzhou, Zhejiang 310022, China
jiyl@zjcc.org.cn

Xiuning Le
Division of Internal Medicine, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4000, USA
XLe1@mdanderson.org

Xiaoling Xu
Postgraduate Training Base Alliance, Wenzhou Medical University, Wenzhou 325035, Zhejiang, China

Department of Radiation Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Zhenmin Road, Shanghai 200433, China
xuxiaoling@tongji.edu.cn

Lisha Ye
Wenjing Wang
Huihui Li
Department of Medical Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, China

Postgraduate Training Base Alliance, Wenzhou Medical University, Wenzhou 325035, Zhejiang, China

*These authors have contributed equally to this work as co-first authors.

Backgrounds

In non-small cell lung cancer (NSCLC), MET gene alterations, such as amplification, exon 14 skipping, fusions, and overexpression, are observed. MET overexpression, the most common alteration at 35%–72% prevalence,[1] can be identified by selecting a suitable cutoff, potentially benefiting treatment and clinical trials. MET amplification occurs in 2%–4% of cases, and exon 14 skipping mutations in 3%–4%,[2] both being actionable alterations. MET fusions are less common, found in only 0.2%–0.3% of lung cancer patients.[3] At present, the primary therapeutic approach for NSCLC patients exhibiting MET alterations involves the use of MET tyrosine kinase inhibitors (MET-TKIs). However, the clinical outcomes achieved with this method have not met expectations. Moreover, challenges persist in the detection of MET alterations, particularly regarding the determination of cut-off values, which complicates the interpretation of test results. Consequently, there is a pressing need to investigate alternative therapeutic strategies for NSCLC cases characterized by MET mutations. One promising avenue for future exploration is the integration of immunotherapy with existing treatment modalities to enhance therapeutic efficacy.

The MET and MET pathways

One of the leading causes of global cancer fatalities is lung cancer. Approximately 85% of all patients have a histological type of NSCLC.[4] The MET gene, recognized as an oncogenic driver in this disease, becomes activated by its natural ligand HGF, thereby triggering other signaling pathways like RAS, NF-κB, PI3K/AKT, and

Table 1. MET mutation types and detection methods.

MET alteration type	Description	Detection methods	Challenges
MET Amplification	Results from polysomy and local gene amplification	NGS, FISH, qRT-PCR	Definitive amplification thresholds challenging to establish
METex14 Skipping	Induced by mutations disrupting the regulatory juxtamembrane domain	Sanger Sequencing, RNA-based NGS, RT-PCR	/
MET Fusions	Arise from chromosomal rearrangements, often involving exon 15 and kinase domains	Hybridization-based technologies, AMP in RNA-NGS, FISH, qRT-PCR	DNA-NGS is less sensitive for detecting fusions
MET Overexpression	Associated with ligand-independent phosphorylation and aberrant signaling activation	IHC	Inconsistent truncation point settings for MET overexpression

AMP, Anchored Multiplex PCR; FISH, Fluorescence in Situ Hybridization; IHC, immunohistochemical; NGS, Next-Generation Sequencing; qRT-PCR, Quantitative Reverse Transcription Polymerase Chain Reaction.

JAK/STAT.[5] These pathways regulate complex physiological processes, including angiogenesis, embryonic development, epithelial-mesenchymal transition, and antiapoptotic signaling.[6]

Variants and detection methods of MET in NSCLC

MET amplification, resulting from polysomy and local gene amplification,[7] can be identified using next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), and quantitative reverse transcription polymerase chain reaction (qRT-PCR; Table 1), although establishing definitive amplification thresholds remains challenging.[8] METex14 skipping, induced by mutations that disrupt the regulatory juxtamembrane domain,[9] leads to hyperactive MET signaling, promoting uncontrolled cell proliferation and potentially oncogenic growth.[10] Kurtis et al.[11] reported that RNA-based methods have a significant advantage in sensitivity compared to DNA-based methods. This advantage is primarily due to the ability of RNA sequencing to bypass the inherent limitations of DNA sequencing technology, thereby more effectively detecting mutations and variations associated with MET. However, the high sensitivity of RNA sequencing also means that it has stricter requirements for the quality of RNA in the samples. The stability of RNA molecules is relatively low and can be easily affected by various conditions, including the methods of sample preservation and processing, all of which can significantly impact the accuracy of sequencing results (Table 1). MET fusions arise from chromosomal rearrangements, predominantly involving exon 15 and downstream kinase domains,[12] and are identified using hybridization-based technologies or anchored multiplex PCR (AMP) in RNA-NGS, with FISH and qRT-PCR as alternative detection methods (Table 1)[13]; DNA-NGS, however, is less sensitive for this purpose. MET overexpression, associated with ligand-independent phosphorylation and aberrant activation of signaling pathways, correlates with tumor metastasis, increased invasiveness, and reduced patient survival.[14] It is assessed using various immunohistochemical antibodies and scoring systems, with a common grading scale of 0–3+ for staining intensity, and the H-score (ranging from 0 to 300) as criteria for identifying overexpression, where a score above 200 typically indicates increased MET expression levels (Table 1).[15] Different detection methods come with their own set of advantages and constraints. In clinical applications, clinicians need to choose the appropriate test for the situation and understand the limitations of the testing methods for accurate interpretation of results. When feasible, integrating a variety of detection methods can augment the sensitivity of the diagnostics.

Current treatment for patients with MET-altered NSCLC

MET tyrosine kinase inhibitors

MET-TKIs can be classified as type Ia, type Ib, or type II. Type Ia relies on binding to a G1163 residue and is susceptible to mutations in this residue, while type Ib has the opposite effect.[16] Both type I and II inhibitors are ATP-competitive TKI inhibitors, but type II inhibitors have greater

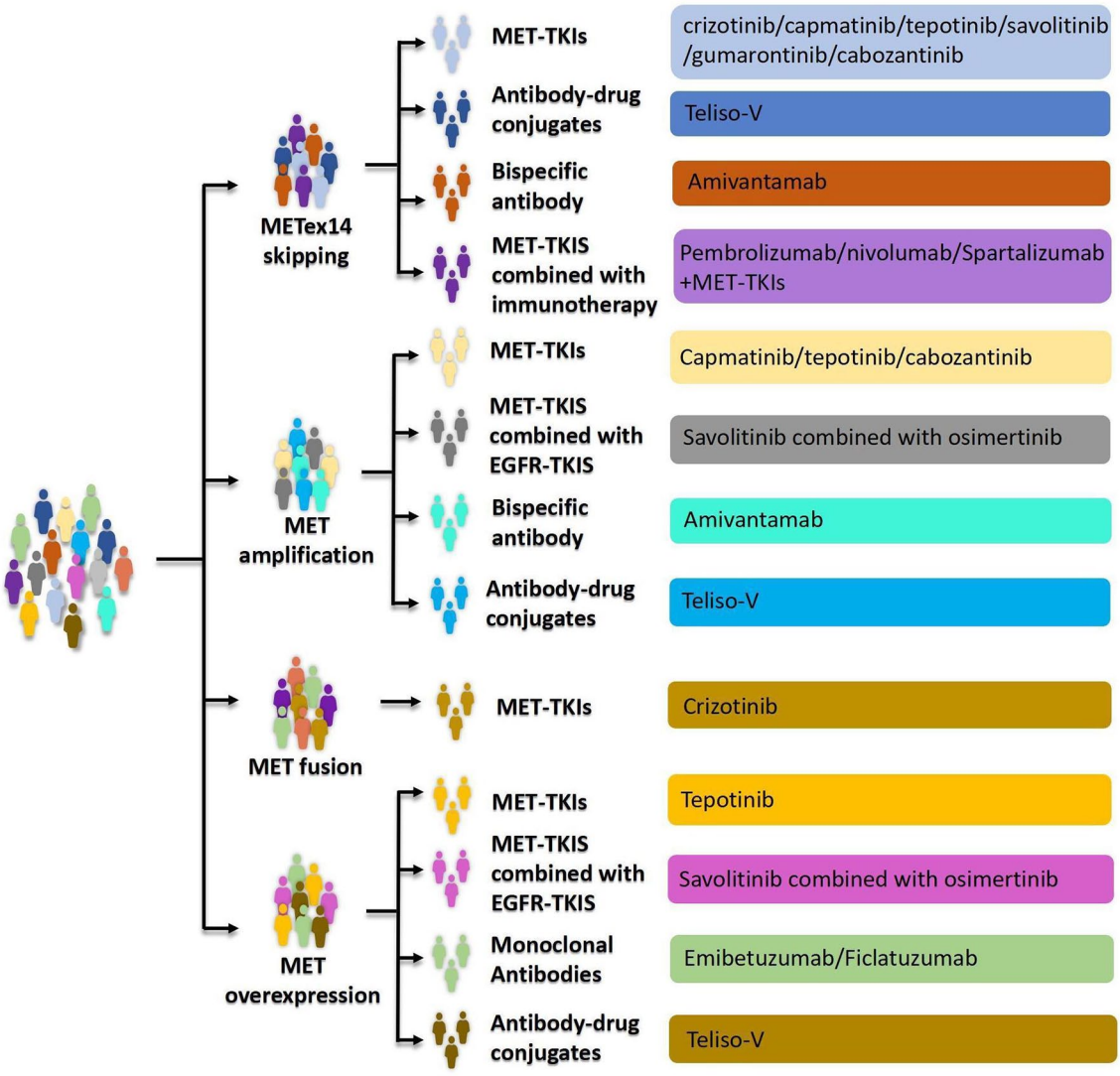

Figure 1. Therapeutic approaches for diverse MET alterations in NSCLC patients. The standard pharmacological interventions for conditions characterized by MET amplification, METex14 skipping, MET fusion, and MET overexpression encompass MET-TKIs (e.g., crizotinib, capmatinib, tepotinib, savolitinib), bispecific antibodies (e.g., amivantamab), ADC drugs (e.g., Teliso-V), and monoclonal antibodies (e.g., emibetuzumab, ficlatuzumab). The concurrent administration of MET-TKIs in conjunction with immunotherapy has been utilized in the treatment of NSCLC presenting with METex14 mutations, while its efficacy in other mutational contexts remains to be elucidated.
NSCLC, non-small cell lung cancer.

potential for slowing down rates and are stronger in kinase specificity than type I inhibitors; this is because type II inhibitors can expose an additional hydrophobic binding site adjacent to the MET ATP binding site by recognizing the inactive conformation of the kinase.[17] MET-TKI are currently widely used in the treatment of NSCLC with MET alterations (Figure 1), including crizotinib, capmatinib, tepotinib, savolitinib, and cabozantinib, among others. A multitude of studies on these drugs are actively underway, with the potential for some to significantly inform clinical guidance on medication use. For instance, studies such as INSIGHT 2 (NCT03940703), SAVANNAH (NCT03778229), and SACHI (NCT05015608) are currently underway to assess the efficacy of tepotinib or savolitinib in combination with osimertinib in patients with

epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) resistance and MET positivity. These studies are expected to provide effective resistance overcoming strategies for MET-driven EGFR-TKI resistant patients. In addition, studies have shown that cabozantinib can compensate for crizotinib's lack of ability to infiltrate the central nervous system, offering greater benefits to patients with brain metastases.[18] Presently, the Phase II clinical study CABinMET (NCT03911193) on cabozantinib for the patients with primary or treated MET-altered (METex14, METamp) NSCLC is underway, anticipated to yield hopeful therapeutic options for this patient group.

Antibody therapy targeting MET

With the increasing understanding of the structure–function relationships of ligands, receptors, and activators, the development of HGF/SF-MET inhibitors for cancer therapy continues to advance. In a phase II randomized controlled clinical study, the combination of the MET monoclonal antibody emibetuzumab with erlotinib significantly prolonged overall survival (OS) (34.3 vs 25.4 months). In a subgroup analysis, the combination therapy was found to have a significant survival benefit in patients with high levels of MET protein overexpression (mPFS: 15 vs 5.4 months; Table 2).[19] Onartuzumab (MetMab), a humanized, monovalent monoclonal antibody targeting MET receptors, primarily inhibits HGF/MET binding without inducing excitatory activity or MET dimerization.[20] In a phase II randomized trial, the combination of onartuzumab and erlotinib was used to treat advanced NSCLC patients. Compared to erlotinib monotherapy alone, the combination therapy significantly improved the median progression-free survival (mPFS) (2.9 vs 1.5 months; Table 2).[21] In addition, therapies targeting the extracellular domain of MET are actively being developed; among them, REGN5093 is an METxMET bispecific antibody (Table 3),[22] and Amivantamab (JNJ-61186372) is also a potential therapeutic drug for MET. Amivantamab is an EGFR-MET bispecific antibody with immune cell targeting activity. In a phase I clinical trial CHRYSALIS (NCT02609776), NSCLC patients carrying METex14 mutations showed a good response to amivantamab treatment. The objective response rate (ORR) reached 33%, with a median PFS of 6.7 months (Table 2).[23] These results provide strong evidence for the potential of amivantamab in treating patients with METex14 mutations.

Antibody–drug conjugates targeting MET

Antibody-drug conjugate (ADC) drugs have some advantages over traditional treatments. They combine the tumor cell-specific targeting ability of monoclonal antibodies with the potent killing activity of the drug through their unique structure and can therefore be tailored to different tumor types and antigen expression levels to enable personalized treatment.[24] Its payload released within the tumor cell not only kills cells expressing the target antigen, but may also affect surrounding tumor cells that do not express the target antigen through a bystander effect. The targeted nature of ADCs helps to reduce the risk of tumor resistance and allows for therapeutic efficacy to be achieved at lower doses, with reduced systemic toxicity and an improved therapeutic window.[25] Particularly importantly, ADC drugs offer new treatment options for patients with tumors that have failed to respond to, or have developed resistance to, conventional or targeted therapies. Teliso-V (ABBV-399) is an ADC composed of the anti-MET monoclonal antibody ABT-700 connected to the microtubule inhibitor Monomethyl auristatin E (MMAE) via a valine–citrulline linker. This drug has been granted Breakthrough Therapy Designation by the US Food and Drug Administration (FDA) for the treatment of EGFR wild-type, nonsquamous NSCLC patients with advanced/metastatic c-MET overexpression and previously treated. Progress has been made in several clinical trials. In a phase I study of 52 patients treated with ABBV-399 $\geqslant$ 1.6 mg/kg every 2 weeks ($n = 28$) or $\geqslant$ 2.4 mg/kg every 3 weeks ($n = 24$), among the 40 evaluable c-MET-positive patients, the ORR was 23%, and the mPFS was 5.2 months (Table 2).[26] A phase Ib study evaluated ABBV-399 in combination with erlotinib in patients with advanced NSCLC who were c-MET-positive. Among 36 evaluable patients, the overall ORR reached 23%, and the median PFS was 5.9 months (Table 2).[27] This study revealed that in EGFR-TKI-treated patients with positive c-MET and EGFR mutations, combination therapy comprising ABBV-399 and erlotinib had good antitumor activity and acceptable toxicity. The current phase II trial aimed to identify the optimal population of NSCLC patients with c-MET overexpression treated with ABBV-399 (phase I) and expand the selected population for further

Table 2. Advancements in main drug therapies for NSCLC with MET alterations.

Category	Drugs	Classify	Trial number	Phase	Types of variation	Subgroup	ORR	mPFS
MET-TKIs	Crizotinib	Type Ia	NCT0058519	Phase II	METex14	/	32% (21/65)	7.3 months[46]
	Capmatinib	Type Ib	NCT02414139	Phase II	METex14	Treatment-naive patients	68% (19/28)	12.4 months[41]
						Previously-treated patients	41% (28/69)	5.4 months[41]
	Savolitinib	Type Ib	NCT02897479	Phase II	METex14	/	49.2% (30/61)	6.8 months[116]
	Tepotinib	Type Ib	NCT02864992	Phase II	METex14	Liquid-biopsy group	48.5% (32/66)	8.5 months[117]
						Tissue-biopsy group	50% (30/60)	11 months[117]
	Gumarontinib	Type Ib	NCT04270591	Phase II	METex14	Treatment-naive patients	71% (31/44)	11.7 months[118]
						Previously-treated patients	60% (21/35)	7.6 months[118]
Antibody therapy targeting MET	Emibetuzumab	Monoclonal antibodies	/	Phase II	MET overexpression	Combination of emibetuzumab and erlotinib	/	20.7 months[19]
						Erlotinib alone	/	5.4 months[19]
	Onartuzumab	Monoclonal antibodies	/	Phase II	MET positive	Combination of onartuzumab and erlotinib	/	2.9 months[21]
						Erlotinib alone	/	1.5 months[21]
	Amivantamab	EGFR-MET bispecific antibody	NCT02609776	Phase I	METex14	/	33% (15/46)	6.7 months[23]
Antibody-drug Conjugates Targeting MET	Teliso-V	ADC	NCT02099058	Phase Ib	MET positive	Combination of Teliso-V and erlotinib	30.6% (11/36)	5.9 months[27]
			NCT02099058	Phase II	MET positive	/	23% (9/40)	5.2 months[26]
			NCT03539536	Phase II	MET overexpression	high MET expression	52.2% (12/23)	/
						medium MET expression	24.1% (7/29)[28]	/

NSCLC, non-small cell lung cancer.

Table 3. Ongoing studies on drug therapies for NSCLC with MET alterations.

Category	Classify	Trial number	Phase	Types of variation	Primary outcome measures
MET-TKIs					
Crizotinib	Type Ia	NCT04084717	Phase II	METex14, MET amplification	RR, PFS, OS
Capmatinib	Type Ib	NCT02750215	Phase II	METex14	ORR
		NCT05110196	Phase IV	METex14	AEs, Percentage of participants with dose modifications, Dose intensity
		NCT04677595	Phase II	METex14	ORR
		NCT05567055	Phase II	METex14, MET amplification	CORR
		NCT05435846	Phase I/Ib	METex14	DLTs
Savolitinib	Type Ib	NCT04606771	Phase II	MET amplification	ORR
		NCT05777278	Phase I/II	METex14	ORR
		NCT05009836	Phase III	MET positive	PFS
		NCT05015608	Phase III	MET amplification	PFS
		NCT03778229	Phase II	MET amplification, MET overexpression	ORR
Tepotinib	Type Ib	NCT06083857	Phase I/II	METex14	IAEs
		NCT03940703	Phase II	MET amplification	DLTs, ORR
		NCT04647838	Phase II	METex14, MET amplification	ORR
		NCT02864992	Phase II	METex14, MET amplification	ORR
Cabozantinib	Type II	NCT03911193	Phase II	METex14, MET amplification	RR
		NCT01639508	Phase II	Increased MET activity	ORR
Merestinib	Type II	NCT02920996	Phase II	METex14	ORR
Antibody therapy targeting MET					
Amivantamab	EGFR-MET bispecific antibody	NCT06083857	Phase I/II	METex14	IAEs
REGN5093	MET-MET bispecific antibody	NCT04077099	Phase I/II	METex14, MET amplification, MET overexpression	AESIs, SAEs, ORR
Antibody-drug Conjugates Targeting MET					
REGN5093-M114	METxMET ADC	NCT04982224	Phase II	MET overexpression	DLTs, TEAEs, SAEs, ORR
Antibody Therapy Targeting the Ligand HGF					
Ficlatuzumab	Monoclonal antibodies	NCT01039948	Phase II	EGFR mutations combined with high MET expression	ORR

AEs, Adverse Events; AESIs, adverse events of special interest; CORR, CNS Overall response rate; DLTs, Dose limiting toxicities; IAEs, Incidence of adverse events; NSCLC, non-small cell lung cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; RR, Response rate; SAEs, Serious adverse events; TEAEs, Treatment-emergent adverse events.

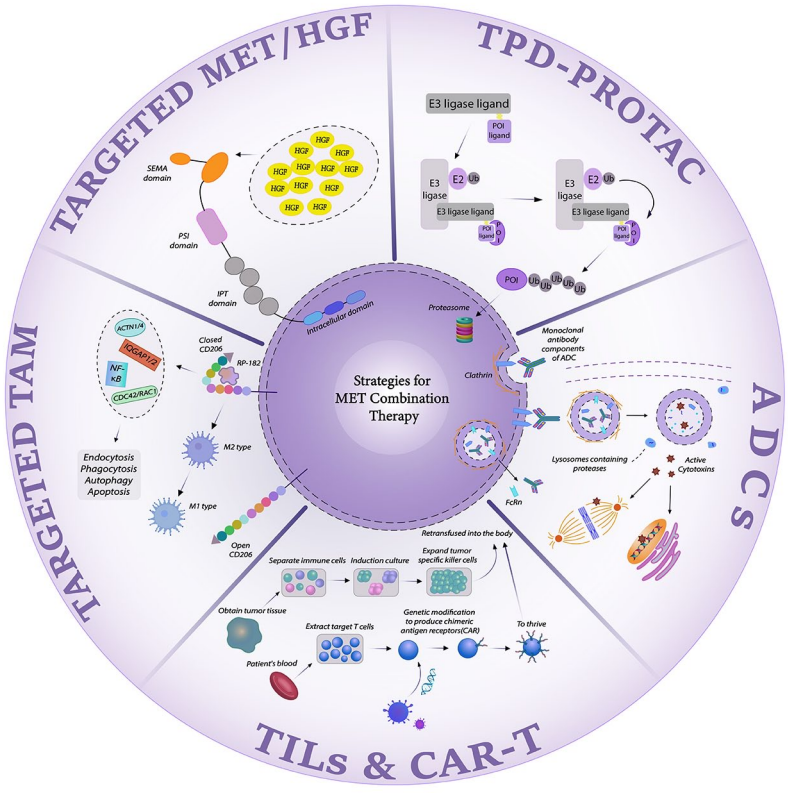

Figure 2. Possible treatment options in combination with immunotherapy. Treatment methods that have the potential to be combined with immunotherapy such as targeted MET/HGF antibodies, and MET- TKIs are designed to intercept different domains of the c-MET receptor. TPD-PROTACs are molecules engineered to induce MET degradation by forming a ternary complex with the POI and an E3 ubiquitin ligase, which triggers ubiquitination and subsequent proteasomal degradation. ADCs deliver cytotoxic payloads to tumor cells through receptor-mediated endocytosis, followed by lysosomal release, leading to cell apoptosis. TIL and CAR-T therapy involve extracting, modifying, and reinfusing immune cells to enhance antitumor activity. In targeted TAM therapy, RP-182 activates signaling pathways that promote phagocytosis and autophagy, as well as providing costimulatory signals for NF-κB activation, thereby aiding in the immune response against tumors.
POI, protein of interest; TAM, tumor-associated macrophages; TILs, tumor-infiltrating lymphocytes; TPD, targeted protein degradation.

evaluation of efficacy (phase II). The latest data were reported at the 2022 American Society of Clinical Oncology (ASCO) Congress: the ORR was 36.5% in the EGFR wild-type nonsquamous NSCLC group, 52.2% in the high c-MET expression group and 24.1% in the medium c-M expression group (Table 2).[28] REGN5093-M114 is an ADC based on REGN5093 that is conjugated with the toxin M24 (a derivative of metformin) through the M114 linker on the surface of the antibody. In vitro experiments, REGN5093-M114 significantly reduced tumor cells in MET-driven EGFR-TKI-resistant patients.[22] A phase II study (NCT04982224) is currently being conducted on patients with MET overexpression to evaluate its clinical efficacy (Table 3), and the data will contribute to the clinical application of the novel therapy.

Antibody therapy targeting the ligand HGF

New drugs targeting HGF (HGF antagonists) or hepatocyte growth factor receptor (HGFR) can block MET signaling at the ligand–receptor level and inhibit overactivation of the MET pathway (Figure 2).[20] Ficlazumab (AV-299) is an anti-HGF monoclonal antibody. In a phase I study, good treatment tolerability was demonstrated when this drug was in combination of an anti-EGFR drug.[29] In another phase II clinical trial involving an Asian

population, the evaluation of ficlatuzumab combined with gefitinib versus gefitinib monotherapy in the treatment of advanced NSCLC was revealed. By analyzing specific subgroups, it was found that the ORR in people with EGFR mutations and high MET protein expression was approximately 20% higher than monotherapy, and the mPFS was 5.5 months longer, with a significant benefit from the combination therapy.[30]

Current problems

Inconsistency between MET mutations and MET overexpression

The overexpression of MET often occurs alongside various cancer-causing mutations, being detected in 35%–72% of NSCLC cases through immunohistochemistry (IHC). However, its significance as a separate prognostic element for this disease remains a topic of debate.[14] Thus far, the use of MET protein expression as a biomarker in targeted treatment for MET via monoclonal antibodies and MET-TKIs has not been successful[12]; moreover, a phase III clinical study (NCT01456325)[31] comparing the efficacy of an MET monoclonal antibody combined with erlotinib versus placebo combined with erlotinib in advanced MET-positive (⩾50% of tumor cells with MET IHC scores of 2+ or 3+) NSCLC patients did not show significant improvement in clinical outcomes. This result may indeed suggest that the impact of MET as the primary biomarker for NSCLC is still unclear.

MET overexpression was correlated with METex14 skipping and MET amplification but was not strongly correlated. The three-center cohort study data of the Lung Cancer Mutation Alliance (LCMC)[32] demonstrated that out of the 71 (39%) MET IHC-positive (H-score⩾200) patients screened, only 1 (2%) was detected among the 3 MET-amplified (MET/CEP7>2.2) patients. In addition, although both (1%) patients with METex14-related alterations were detected, considering the high frequency of MET IHC positivity in lung cancer and because METex14-mutated lung cancer is usually IHC positive, MET IHC is a poor screening strategy for detecting METex14 mutations.[33] Because of the low number of patients, exhibiting MET amplification and METex14 mutation, coupled with the absence of MET fusion data, necessitates the need for additional assay data to the significance of MET overexpression as a screening tool for identifying MET alterations.

MET amplification and cut-off points

There are currently various methods available for detecting changes in MET copy number and MET expression, but unfortunately, the cut-off points for defining MET amplification and MET overexpression vary according to each detection method. MET amplification is mainly defined through two methods of FISH, which is the gold standard for MET amplification detection. The first method relies on the gene copy number (GCN) and defines MET amplification as the presence of five or more MET copies per cell (METGCN⩾5)[34]; other studies have defined this as METGCN⩾6[35] or METGCN⩾15.[36] However, MET amplification includes both true amplification and polyploid amplification and cannot be distinguished by GCN-dependent methods. Polyploid amplification of MET occurs when MET occurs with a regional or local increase in copy number on a specific arm of chromosome 7 (located at 7q31). Therefore, taking the ratio of MET to CEP7 (centromere seven counting probe) is another more accurate method in the absence of chromosome duplication.[37] Generally, MET/CEP7⩾2.0 is used to define focal amplification, while METGCN⩾5 with MET/CEP7 <2 is considered polyploid amplification.[38] Numerous studies are delving into the identification of cutoff points that would benefit patients, thereby refining detection methodologies. In one such study, the efficacy of crizotinib was assessed across varying degrees of MET gene amplification[39]: low-level amplification (MET/CEP7 between 1.8 and 2.2), moderate-level amplification (ratio between 2.2 and 5), and high-level amplification (ratio above 5). The experimental data[40] revealed that patients with high-level amplification had the highest ORR, reaching 50%, whereas the ORR for patients with low and moderate amplification were 33% and 20%, respectively. In subsequent updates to this study, the threshold between moderate and high amplification was adjusted to an MET/CEP 7 ratio of 4, and it was found that patients with high-level amplification consistently achieved the best therapeutic outcomes (ORR of 40%, with an mPFS of 6.7 months). Similar conclusions have been drawn from other studies.[41,42] This suggests that, in general, patients with higher levels of MET amplification respond better to MET inhibitors. Establishing a relatively high cutoff value helps to identify a patient population that is more sensitive to the medication and tends to have better therapeutic outcomes, although this may exclude some patients who could potentially benefit. The

"NCCN Clinical Practice Guidelines in Oncology – Non-Small Cell Lung Cancer (Version 4.2024)"[43] recommend defining high-level MET amplification as GCN⩾10 detected by NGS. Conversely, setting a lower cutoff value to include more patients might encompass many who do not respond to the treatment. For instance, in the onartuzumab study, half of the patients selected based on MET expression levels participated in the research, a proportion that significantly exceeds the likely number of patients who are genuinely reliant on the MET pathway.[44]

It has to be said that the level of MET expression, as a continuous variable, has a certain degree of arbitrariness in the setting of any cutoff point, rather than being entirely based on biological mechanisms.[2] In clinical practice, it may be necessary to select cutoff points in a more personalized manner, establishing inclusive thresholds. Reducing interobserver variability in FISH interpretation through digital pathology or confirming MET amplification through orthogonal experiments may be effective solutions.[8]

MET-targeted therapy exhibits limited PFS and susceptibility to drug resistance in NSCLC

Since PAIK et al.[45] first reported crizotinib and cabozantinib as third-line treatment options for patients with stage IV lung adenocarcinoma carrying METex14 mutations in a small retrospective series of studies in 2015, many studies targeting MET-TKIs have been initiated in the field since, also mostly focusing on METex14 mutations. However, many clinical studies related to MET-TKIs have shown that although the ORR is high, PFS is not ideal. For example, a subsequent additionally reported phase I clinical trial by PAIK et al. (Profile 1001)[46] showed an ORR of 32.3%, a duration of response (DOR) of 9.1 months, and a PFS of only 7.3 months. MET amplification has been shown to exhibit sensitivity to MET-TKI, but there is a lack of studies based on large samples to further clarify this.[2] In a clinical study utilizing capmatinib for the treatment of NSCLC patients with METex14 mutations or MET amplifications, the ORR was 68% and the PFS was 12.4 months for untreated patients with METex14 mutations. For patients with MET amplification, those with a GCN of 10 or higher had an ORR of 40% and a PFS of 4.2 months; however, patients with a GCN below 10 exhibited a limited therapeutic response.[41] This study not only pointed out that the level of MET amplification is an important factor influencing the response to treatment, but also revealed a limited PFS. In patients with lung cancer, MET fusion is a rare event. A study found that patients with MET fusions responded to crizotinib treatment, with PFS ranging from 4 to 14 months.[3]

Drug resistance significantly impedes the efficacy of MET inhibitors, with research primarily centered on MET-TKIs. This resistance is categorized into primary and secondary forms, yet the underlying mechanisms remain not fully understood. Studies have shown that the presence of MET gene alterations accompanied by other co-mutated genes may be one of the primary resistance mechanisms, such as PIK3CA mutations.[47] The occurrence of secondary drug resistance may be due to changes in the MET domain after initial treatment with MET inhibitors. Type I and type II TKIs act at different sites on the MET molecule, and their resistance mutations occur at different residues. For example, a study reported that a patient with METex14 had an acquired mutation in the MET kinase domain D1228N during the progression of crizotinib treatment.[48] Combining MET-TKIs with immunotherapy to improve PFS and overcome drug resistance is a promising therapeutic direction. In recent years, research on organoids has developed rapidly, and using organoids to screen sensitive drugs may be an effective tool for further studying MET-TKIs.[49]

Features of the TIME in patients with MET-altered NSCLC

Antigen presentation and immunogenicity characteristics of TIME

The tumor mutational burden (TMB) is an important indicator of the number of mutations in cancer. The presence of high TMB suggests that tumor cells have undergone numerous mutations, leading to the creation of additional new antigens that are immunogenic and more likely to activate T-cell responses. After analyzing The Cancer Genome Atlas (TCGA) online dataset, a study revealed that patients with MET amplification had a significantly greater TMB than did patients without MET alterations. These findings could lead to the use of MET amplification as a representative predictive biomarker for immunotherapy, providing new perspectives and evaluation tools for clinical treatment.[50] A comparative

analysis was carried out for 138 patients with METex14-mutant and 5162 patients with MET-WT NSCLC at the 2022 World Conference on Lung Cancer. Among METex14 lung cancer patients, the proportion of patients with high TMB (TMB-H, defined as TMB $\geqslant$ 10 mt/Mb) was significantly lower, at 16.3%, than that of patients with wild-type MET.[51] Another study targeting three groups of NSCLC patients with oncogene alterations (a total of 4189 patients) revealed similar characteristics of TMB in the METex14 cohort.[52] Thus, it is evident that even within the MET mutation spectrum, the immunological features vary among different types due to their distinct underlying characteristics. This diversity has led to a lack of consensus on the efficacy of immunotherapy in studies focusing on NSCLC patients with MET alterations. This difference may be due to the expansion of myeloid-derived suppressor cells (MDSCs) by mesenchymal stem cells (mediated by downstream STAT3 phosphorylation of the HGF/c-MET signaling pathway). MDSCs can inhibit cytokine production, inhibit T-cell proliferation, and significantly inhibit immune cell responses, NK cell cytotoxicity, and dendritic cell (DC) antigen presentation.[53] Another possible potential reason is the correlation of high MET copy number with lower stimulation of interferon gene (STING) signaling. The MET gene weakens the immune system's ability to recognize and attack tumors by inhibiting the STING signals, reducing the immunogenicity of tumors and thus affecting the effectiveness of immunotherapy.[54] Overall, although MET mutations are linked to a higher TMB in NSCLC patients, these mutations reduce the immunogenicity of tumors by altering the immune microenvironment, which may be the reason for the poor efficacy of immunotherapy. This discovery suggests that for NSCLC patients with MET alterations, a deep understanding of the characteristics of their immune microenvironment is crucial for optimizing immunotherapy regimens.

Infiltration of immune cells

CD8+ T cells are the most essential component of tumor-infiltrating lymphocytes (TILs) when killing tumor cells in the body,[55] and a low infiltration level of CD8+ T cells in lesions is closely related to poor prognosis.[56] A study showed a significant increase in the number of TILs in patients with MET-altered tumors, and MET amplification was independently correlated with the infiltration levels of CD8+ T cells and TILs in tumors.[57]

Among immune cells, tumor-associated macrophages (TAMs) have the highest infiltration rate in the tumor microenvironment (TME). TAMs can stimulate invasion, proliferation, and metastasis, as well as tumor angiogenesis and TME immunosuppression, in NSCLC cells to promote tumor occurrence and development.[58] Therefore, NSCLC patients with higher levels of TAM infiltration often have poorer prognoses,[59] indicating that TAMs play an important role in the occurrence and development of NSCLC. Macrophages are highly malleable and can differentiate specifically into M1 and M2 phenotypes in different tissue environments and produce different effects. M1-type macrophages have antitumor activity and help activate adaptive immune and inflammatory responses, while M2-type macrophages promote tumor occurrence and development by inhibiting the immune function of the TME and promoting angiogenesis, tissue reconstruction, and damage repair.[60] Research has shown that activation of the downstream PI3K pathway by the HGF/c-MET signaling pathway can lead to the dependent induction of Arg-1 expression, which transforms tumor-inhibiting M1-type macrophages into tumor-promoting M2-type macrophages.[61] CSF-1R is a protein that mediates the survival of macrophages in tumor tissue, and its inhibition is considered a therapeutic strategy for eliminating TAMs. However, studies have shown that although CSF-1R inhibitors can effectively eliminate TAMs, they can cause tumor-associated fibroblasts to release more of the chemokine CXCL1, thereby recruiting more immunosuppressive polymorphonuclear MDSCs and promoting tumor growth.[62]

Tregs are a subgroup of T cells that can downregulate or inhibit the induction and proliferation of effector T cells and participate in regulatory immunity. A study revealed that under HGF induction, monocytes can differentiate into tolerant DCs. In addition, HGF also enhances the ability of DCs to produce the immunosuppressive cytokine IL-10. These findings further confirm that the HGF/c-MET pathway is involved in Treg accumulation.[63] Tregs can upregulate immunosuppressive signals, such as T-cell immunoglobulin and mucin domain-3 (TIM-3) and lymphocyte activation gene 3 (LAG-3),[64] to produce the immunosuppressive cytokines IL-10 and TGF-β,

which can inhibit the activity of CD8+ T cells. In addition, Treg cells can also contact and interact with DCs, causing DC depletion, further leading to reduced activation of CD8+ T cells and inhibiting CD8+ T-cell-mediated cytotoxicity.[65] Moreover, as inhibitory cytokines of NK cells, TGF-β and IL-10 can inhibit the migration of NK cells to the TME and its antitumor effects, leading to NK cell dysfunction.[66]

Therefore, MET mutations cause extensive infiltration of immunosuppressive cells, including Tregs, TAMs, MDSCs, etc., as well as depletion of immune-activated cells, inhibition of the antitumor immune response, and therapeutic methods targeting the HGF/c-MET pathway are effective strategies.

Tumor cells evade immune killing

PD-1 and PD-L1 play important negative regulatory roles in the immune response to tumors, enabling tumor cells to successfully evade immune system attacks. Research has shown that in lung adenocarcinoma patients, MET mutations are significantly positively correlated ($p < 0.001$) with high PD-L1 expression.[67] According to previous studies, there is a positive correlation between PD-L1 expression and MET amplification in NSCLC patients,[68] and patients with METex14 skipping have a high positivity rate.[69] These studies have some guiding significance for the application of immune checkpoint inhibitors (ICIs) in patients with MET-altered NSCLC. However, as previously mentioned, different types of MET mutations exhibit similar yet distinct immunological characteristics, which suggests that for patients with genomic alterations in the MET gene, selecting individuals based on biomarkers associated with immunotherapy prognosis can more precisely identify those who are likely to benefit.

TAMs are also interrelated with the expression of PD-L1; almost all PD-1$^+$ TAMs express the M2 type, while PD-1$^-$ TAMs mainly express the M1 type, and high expression of PD-L1 can induce M2 polarization of TAMs.[70] M2-type TAMs can inhibit NK cell activity and promote the expression of PD-L1 and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), hindering effector T-cell infiltration by blocking immune checkpoints[71]; however, the secretion of TGF-β upregulates Tregs, the Foxp3 gene induces CTLA-4 expression on the surface of Tregs, and CTLA-4 binds to CD80 and CD86 on antigen-presenting cells, resulting in their downregulation and inhibition of T-cell activation.[72] In addition, the surface-characteristic marker molecule CD25 has a high affinity for IL-2 and limits the activation and proliferation of effector T cells by binding to IL-2.[73] Most tumor-infiltrating Tregs exhibit increased PD-1 expression, thereby inducing immunosuppression through the interaction of PD-1 and PD-L.[74] Furthermore, MDSCs can also induce T-cell tolerance by expressing inhibitory receptors such as PD-L1 and CTLA-4.[75]

In summary, MET mutations promote immune escape mechanisms by inducing and recruiting immunosuppressive cells and increasing the expression of various immunosuppressive molecules. By blocking these immunosuppressive mechanisms, the underlying antitumor immune response can be restored. Immunotherapy with ICIs, such as CTLA-4 monoclonal antibodies and PD-1 or PD-L1 monoclonal antibodies, can rescue cytotoxic effector CD8+ T-cell dysfunction and kill tumor cells.

Opportunities for immunotherapy via the MET pathway

Immunotherapy

ICIs have become one of the first-line treatment options for NSCLC patients who lack driver mutations.[76] Retrospective studies indicate that patients with NSCLC harboring KRAS, BRAF mutations, or co-occurring TP53 mutations derive more favorable outcomes from ICIs, whereas those with EGFR, ALK, or MET mutations exhibit suboptimal benefits from immunotherapy.[77] However, notably, certain studies have demonstrated a positive correlation between PD-L1 expression and MET amplification in NSCLC patients, suggesting that ICIs may be effective in treating MET-amplified tumors.[68] In patients with NSCLC harboring MET exon 14 skipping, the efficacy of immunotherapy remains a contentious issue. The IMMUNOTARGET study[78] indicated that patients with MET-mutated subgroups, including MET amplification and MET exon 14 skipping mutations, derive relatively limited clinical benefits from immunotherapy, with an ORR of 16% and an mPFS of 3.4 months. A study specifically targeting MET exon 14 skipping also reported a similar ORR of 17% and an mPFS of 1.9 months,[69] consistent with another study's finding that NSCLC patients

with MET mutations may have a lower response to immunotherapy, although the sample size of that study was small.[79] Despite the aforementioned studies showing that patients with MET genomic alterations treated with ICIs have an ORR of less than 20%, suggesting that ICI therapy has some efficacy but is not highly desirable, a retrospective study (GFPC 01-2018)[80] reported a higher ORR. In this study, 30 patients with MET exon 14 skipping treated with ICIs achieved an ORR of 35.7% and an mPFS of 4.9 months. Researchers believe that this may be related to the relatively low number of lines of ICI treatment (63% were first- or second-line treatments) and the higher proportion of patients with high PD-L1 expression (⩾50%) included in the study (37%). Further analysis of the three GFPCs also revealed a higher ORR, which was 43%.[81] This suggests that additional biomarker data are needed in order to determine which patients are most likely to benefit from ICIs.

In recent years, a study[82] has reported a case of an NSCLC patient with an MET exon 14 skipping mutation who experienced a brief period of PFS and rapidly developed resistance following treatment with crizotinib. Upon switching to a regimen combining immunotherapy with chemotherapy, the patient's PFS was extended to 15.0 months. Another study also found that chemoimmunotherapy prolonged PFS compared to chemotherapy.[83] This outcome suggests that the chemoimmunotherapy approach may enhance patient benefit. A recent retrospective study[84] has further corroborated this conclusion. The study found that in the subgroup of patients with MET mutations, including MET amplification and MET exon 14 skipping, the ORR to first-line chemoimmunotherapy was 60%, with an mPFS of 6.2 months. In the second-line treatment, the ORR was lower, at 30.8%, with a median PFS of 5.7 months, and both first- and second-line treatments demonstrated manageable safety profiles.

Immunotherapy combined with targeted therapy

Given the suboptimal outcomes of monotherapy with ICIs in patients with MET-mutated NSCLC, a combination or sequential approach with targeted therapies may represent a promising strategy. Preclinical research utilizing lung cancer cell lines and models from other cancer types has demonstrated that MET inhibitors can reduce the number of neutrophils in tumors and draining lymph nodes that increase reactively due to immunotherapy. These neutrophils rapidly acquire immunosuppressive characteristics within the T-cell inflammatory microenvironment and limit the expansion and effector functions of T cells. By modulating the behavior of immune cells in the tumor microenvironment, particularly neutrophils, MET inhibitors enhance the antitumor immune response mediated by T cells, thereby improving the efficacy of cancer immunotherapy.[85] However, combination therapy may be associated with more serious adverse effects. Several clinical trials have attempted to combine EGFR-TKIs or ALK-TKIs with PD-1/PD-L1 monoclonal antibodies; however, these endeavors have been unsuccessful due to a higher incidence of adverse events, such as interstitial pneumonia and hepatic injury.[86,87] Furthermore, two clinical trials exploring the combination of ICIs with MET-TKIs (NCT04323436, NCT04139317) were prematurely terminated due to toxicity associated with the combined therapy. In one of these trials, out of 51 patients who received the combined treatment, 19 (37.3%) had to discontinue therapy, and there were four suspected treatment-related fatalities.[88] Future research will continue to explore the potential of the combination of ICIs and MET-TKIs, aiming to provide new therapeutic strategies for patients with lung cancer harboring MET alterations. Concurrently, it is imperative to closely monitor the safety profiles of these medications.

Immunotherapy combined with ADC drugs

Previously reported ADC drugs are often associated with dose-limiting toxicity, but the emergence of trastuzumab deruxtecan (DS-8201), a new ADC drug designed using a novel linker peptide-loading technology, has overcome the limitations of the previous generation of compounds and has a synergistic attenuating effect, heralding the arrival of the next generation of ADCs and showing potential for combination with PD-1/L1. Datopotamab deruxtecan (Dato-DXd) is an innovative ADC designed to target human trophoblast surface antigen 2 (TROP2). This drug consists of multiple components, including humanized anti-TROP2 IgG1 monoclonal antibodies, potent topoisomerase I inhibitors that can be effectively loaded, and a stable tetrapeptide-cleavable linker.[89] At the 2023 ASCO Congress, the midterm analysis results of the clinical study TROPION-Lung02 (NCT04526691) were announced, which evaluated the efficacy of Dato-DXd + pembrolizumab

dual and Dato-DXd + pembrolizumab + platinum-based chemotherapy triple in the treatment of newly diagnosed advanced/metastatic NSCLC patients without driver gene mutations. The results showed that the ORRs were 50% and 57%, respectively.[90] Research on TROPION-Lung04 (NCT04612751), TROPION-Lung07, and TROPION-Lung08 (NCT05215340) is currently underway to further evaluate the potential of Dato-DXd in combination with immunotherapy.[91,92] As a "highly effective, targeted chemotherapy" drug, ADC drugs hold promise in exerting synergistic effects when combined with immunotherapy and could become a new direction for next-generation tumor treatment.

Immunotherapy combined with targeted protein degradation

Targeted protein degradation (TPD) is an emerging therapeutic approach with enormous therapeutic potential. For certain proteins that are difficult to target with conventional small molecules, TPD can alter cellular protein homeostasis mechanisms.[93] PROTAC is a bifunctional small molecule composed of two ligands covalently linked by linkers of 5~15 carbon atoms or other atoms; one ligand recruits and binds to the cancer cell-dependent protein of interest (POI), while the other recruits and binds to the E3 ubiquitin ligase.[93] PROTAC proteins simultaneously bind to POI and ligases, leading to ubiquitination of the POI and subsequent degradation by the ubiquitin–proteasome system (UPS). Following degradation, the PROTAC is recycled to target another copy of the POI (Figure 2).[94] PROTAC technology has several advantages over traditional small molecule inhibitors due to its unique mechanism of action. Unlike traditional inhibitors that rely on the active site of target proteins, PROTACs are able to degrade proteins that lack active sites or are difficult to target by traditional means, such as transcription factors and other non-enzymatic proteins, effectively solving the problem of "undruggable." In addition, the catalytic properties of PROTACs allow a single molecule to degrade multiple target proteins in a cyclic manner, reducing the dependence on prolonged drug exposure and sustained high drug concentrations. Compared to non-catalytic, occupation-driven mechanisms of drug action, PROTAC molecules can act at lower doses, reducing the risk of side effects. They also have the advantage of a lower probability of resistance development and a more rapid efficacy response.[95] Two studies have evaluated c-MET PROTACs via the multitargeted kinase inhibitor foretinib, which includes two different E3 ubiquitin ligases, von Hippel–Lindau (VHL) recruitment and cereblon (CRBN) recruitment; both of these studies revealed that foretinib-based c-MET PROTACs effectively degrade c-MET, inhibit tumor cell proliferation, and counter the increased c-met stability of exon 14 deletion and resistance to HGF-mediated degradation.[96] These findings suggest that the application of PROTACs in patients with MET-altered NSCLC may have considerable potential. Subsequently, other studies have designed, synthesized, and evaluated highly potent orally active c-MET PROTACs using tepotinib and thalidomide, which have higher pharmacological activity, broader selectivity, and lower cytotoxicity than previously reported.[97] Targeting immunosuppressive molecules on TAMs is also a promising therapeutic approach that can effectively inhibit endocytosis by interfering with the phagocytic receptor MerTK. This process can lead to the accumulation of apoptotic cells in tumor cells, triggering a type I interferon response and ultimately enhancing antitumor immunity. In addition, other emerging TPD technologies, including lysosome-targeting chimaera, antibody-based PROTAC (AbTAC), autophagy-targeting chimaera (AUTAC), autophagosome-tethering compound (ATTEC), molecular glue, photocontrolled PROTACs, and hydrophobic labeled small molecules, are also important additions to the chemical regulation of intracellular protein homeostasis.[98]

Targeted treatment of TAMs

Given that MET mutations are significantly associated with high PD-L1 expression and that high PD-L1 expression can induce M2 polarization of TAMs,[67,70] MET mutations can promote the polarization of TAMs from the M1 to M2 phenotype through high PD-L1 expression. One of the key characteristics of macrophages is their plasticity, which allows them to alter their phenotype in response to the tumor microenvironment; therefore, the repolarization strategy of reprogramming TAMs to an antitumor phenotype is very promising in tumor therapy. RP-182 is a synthetic 10-mer amphiphilic analog of a host defense peptide that selectively induces a conformational switch to the mannose receptor CD206 expressed on M2-type TAMs, reprogramming M2-type TAMs to the antitumor M1 type (Figure 2).[99] Combination therapy comprising RP-182 expression and chemotherapy or ICIs may be an effective strategy for inhibiting tumor growth and prolonging survival.

In addition, targeting immunosuppressive molecules on TAMs is an effective method that can selectively inhibit endocytosis by blocking the phagocytic receptor MerTK, leading to the accumulation of apoptotic cells in tumor cells and triggering a type I interferon response, enhancing antitumor immunity.[58] PD-1-PD-L1 therapy can act directly on macrophages or synergistically with anti-MerTK antibody therapy to treat tumor-bearing mice and stimulate T-cell activation.[100]

Adoptive cell immunotherapy

TIL therapy refers to the isolation of infiltrating lymphocytes (TILs) from tumor tissue; these cells are cultured and amplified in vitro before being reintroduced into the body (Figure 2). TIL therapy has the advantages of multiple targets, tumor targeting, and minimal side effects and has unique advantages in the treatment of solid tumors.[101] In a phase I clinical trial,[102] 20 patients with advanced NSCLC were administered TIL or IL-2 along with nivolumab after lymphodepletion, 11 of the 13 evaluable efficacy patients experienced a decrease in tumor burden, 3 responded, and 2 achieved a complete response after 1.5 years. Studies have shown that the immune system's response to neoantigens formed by mutations and the subsequent development of tumor-specific lymphocytes increase the likelihood of benefiting from TIL therapy in patients with NSCLC with a high mutational burden, such as those with MET amplification.[103] TIL therapy for solid tumors has unique advantages, but its promotion and popularization face some challenges, mainly including expensive and time-consuming tissue collection and production processes, difficulties in achieving TIL standardization for different patients, and difficulties in selecting prognostic markers. There is still room for further improvement and application of TIL therapy.[101]

CAR-T-cell therapy is a novel therapy that involves the genetic modification of specific tumor antigens and precisely kills tumor cells. CAR-T-cell-targeting c-MET has been developed and verified for its specific killing activity against tumor cells.[104] However, CAR-T-cell therapy for lung cancer, while potentially effective, faces numerous challenges in its widespread use. These include severe targeted toxicity, antigen evasion, and CAR-T-cell persistence.[105] Innovative CAR designs are urgently needed to be developed. CAR-NK therapy appears to have a more favorable safety profile compared to CAR-T-cell therapy, as demonstrated in a clinical trial where no adverse immune-related events were associated with CAR-NK-cell therapy,[106] suggesting that it has certain therapeutic potential. However, the inherent characteristics of NK cells, such as increased difficulty in amplification, isolation, and genetic engineering compared to those of T cells, as well as limited persistence in vivo after infusion, remain unresolved.[107]

Biomarker discovery and patient selection

TMB, microsatellite instability (MSI), and PD-L1 expression are commonly used biomarkers in the field of immunotherapy. Studies have confirmed that MSI can serve as a predictive biomarker for the efficacy of immunotherapy.[108,109] However, a retrospective study has indicated that in NSCLC patients with rare driver genes such as BRAF, MET, RET, HER2, etc., the MSI status is mostly microsatellite stable, similar to the overall situation in lung adenocarcinoma.[110] This suggests that in the population of NSCLC patients with MET mutations, the MSI status may not be as significantly predictive of the efficacy of ICIs as it is in MSI-High tumors.

Regarding PD-L1 expression, there is disagreement among multiple studies. In the GFPC study, the higher ORR may be related to the higher proportion of patients with PD-L1 expression$\geqslant$50% (37%).[80] However, another study has suggested that the efficacy of immunotherapy is not directly related to PD-L1 expression but is associated with TP53 mutations.[83] In addition, a meta-analysis did not observe significant differences in PD-L1 expression among patients with different levels of MET expression,[111] but this finding should be interpreted with caution due to the small number of studies included. It is worth noting that PD-L1 expression is correlated with the specific gene expression characteristics of CD8+ T cells,[112] and combining PD-L1 expression with the infiltration of CD8+ T cells in tumor tissue may improve the accuracy of predicting the efficacy of ICIs.[113]

As for the research results on TMB, they also show certain differences. A studies show no difference in TMB between mutated and wild types,[114] while another study found that TMB in mutated types is lower than in wild type.[69] In addition, the expression level of MET itself is also related to the efficacy of immunotherapy. Studies have found that patients with a high number of

MET copies respond poorly to ICIs.[54,115] These findings suggest that for patients with MET genomic alterations, screening based on prognostic biomarkers related to immunotherapy may help to more accurately identify the population that can benefit from the treatment.

Conclusion

MET mutations reshape the immune microenvironment of NSCLC through intricate mechanisms, including the immunogenicity of the TIME, depletion of immune-activated cells, infiltration of immunosuppressive cells, and evasion of immune killing, affecting the response of patients to immunotherapy. The application of immunotherapy in patients with MET-altered NSCLC holds promise, yet monotherapy presents numerous challenges. Combination therapy offers the potential to overcome these limitations and unlock the full potential of immunotherapy in this setting.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Lisha Ye: Conceptualization; Writing – original draft; Writing – review & editing.

Wenjing Wang: Writing – review & editing.

Huihui Li: Writing - review & editing.

Yongling Ji: Supervision; Writing – review & editing.

Xiuning Le: Writing – review & editing.

Xiaoling Xu: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Acknowledgments

None.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by Zhejiang Provincial Natural Science Foundation of China (Grant No. LTGY23H160011), Program of Province TCM Sci-Tech Plan (Grant No. 2024ZL298), Shanghai Municipal Science and Technology Innovation Action Plan (23Y11908077), Shanghai Pulmonary Hospital Institutional Project (FKLY20006), Establishment and Application of Precision Diagnosis and Treatment System for Thoracic Tumors, and Beijing Xisike Clinical Oncology Research Foundation (Grant No. Y-Q201802-074).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

ORCID iD

Xiaoling Xu https://orcid.org/0000-0003-0618-494X

References

1. Salgia R. MET in lung cancer: biomarker selection based on scientific rationale. *Mol Cancer Ther* 2017; 16: 555–565.
2. Sacco JJ and Clague MJ. Dysregulation of the Met pathway in non-small cell lung cancer: implications for drug targeting and resistance. *Transl Lung Cancer Res* 2015; 4: 242–252.
3. Sun D, Wu W, Wang L, et al. Identification of MET fusions as novel therapeutic targets sensitive to MET inhibitors in lung cancer. *J Transl Med* 2023; 21: 150.
4. Herbst RS, Morgensztern D and Boshoff C. The biology and management of non-small cell lung cancer. *Nature* 2018; 553: 446–454.
5. Owusu BY, Galemmo R, Janetka J, et al. Hepatocyte growth factor, a key tumor-promoting factor in the tumor microenvironment. *Cancers (Basel)* 2017; 9: 35.
6. Ma PC, Maulik G, Christensen J and Salgia R. c-Met: structure, functions and potential for therapeutic inhibition. *Cancer Metastasis Rev* 2003; 22: 309–325.
7. Drilon A, Cappuzzo F, Ou SHI, et al. Targeting MET in lung cancer: will expectations finally be MET? *J Thorac Oncol* 2017; 12(1): 15–26.
8. Remon J, Hendriks LEL, Mountzios G, et al. MET alterations in NSCLC-current perspectives

and future challenges. *J Thorac Oncol* 2023; 18: 419–435.

9. Lu X, Peled N, Greer J, et al. MET Exon 14 mutation encodes an actionable therapeutic target in lung adenocarcinoma. *Cancer Res* 2017; 77: 4498–505.
10. Socinski MA, Pennell NA and Davies KD. MET exon 14 skipping mutations in non–small-cell lung cancer: an overview of biology, clinical outcomes, and testing considerations. *JCO Precis Oncol* 2021; 5: PO.20.00516.
11. Davies KD, Lomboy A, Lawrence CA, et al. DNA-Based versus RNA-based detection of MET exon 14 skipping events in lung cancer. *J Thorac Oncol* 2019; 14: 737–741.
12. Heydt C, Ihle MA and Merkelbach-Bruse S. Overview of molecular detection technologies for MET in lung cancer. *Cancers (Basel)* 2023; 15: 2932.
13. Zheng Z, Liebers M, Zhelyazkova B, et al. Anchored multiplex PCR for targeted next-generation sequencing. *Nat Med* 2014; 20: 1479–1484.
14. Recondo G, Che J, Jänne PA, et al. Targeting MET dysregulation in cancer. *Cancer Discov* 2020; 10: 922–934.
15. Mignard X, Ruppert A-M, Antoine M, et al. c-MET overexpression as a poor predictor of MET amplifications or exon 14 mutations in lung sarcomatoid carcinomas. *J Thorac Oncol* 2018; 13: 1962–1967.
16. Bahcall M, Paweletz CP, Kuang Y, et al. Combination of type I and type II MET tyrosine kinase inhibitors as therapeutic approach to prevent resistance. *Mol Cancer Ther* 2022; 21: 322–335.
17. Zhang J, Yang PL and Gray NS. Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* 2009; 9: 28–39.
18. Klempner SJ, Borghei A, Hakimian B, et al. Intracranial Activity of Cabozantinib in MET Exon 14-Positive NSCLC with Brain Metastases. *J Thorac Oncol* 2017; 12: 152–156.
19. Scagliotti G, Moro-Sibilot D, Kollmeier J, et al. A randomized-controlled phase 2 study of the MET antibody emibetuzumab in combination with erlotinib as first-line treatment for EGFR Mutation-Positive NSCLC Patients. *J Thorac Oncol* 2020; 15: 80–90.
20. Gelsomino F, Facchinetti F, Haspinger ER, et al. Targeting the MET gene for the treatment of non-small-cell lung cancer. *Crit Rev Oncol Hematol* 2014; 89: 284–299.
21. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2013; 31: 4105–4114.
22. Oh SY, Lee YW, Lee EJ, et al. Preclinical study of a biparatopic METxMET antibody-drug conjugate, REGN5093-M114, overcomes MET-driven acquired resistance to EGFR TKIs in EGFR-mutant NSCLC. *Clin Cancer Res* 2023; 29: 221–232.
23. Leslie M. Amivantamab emerges positively from Its "Chrysalis." *Cancer Discov* 2022; 12: OF2.
24. Passaro A, Jänne PA and Peters S. Antibody-drug conjugates in lung cancer: recent advances and implementing strategies. *J Clin Oncol* 2023; 41: 3747–3761. https://doi.org/10.1200/JCO.23.00013.
25. Fu Z, Li S, Han S, et al. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduct Target Ther* 2022; 7: 93.
26. Camidge DR, Morgensztern D, Heist RS, et al. Phase I Study of 2- or 3-week dosing of telisotuzumab vedotin, an antibody-drug conjugate targeting c-Met, monotherapy in patients with advanced non-small cell lung carcinoma. *Clin Cancer Res* 2021; 27: 5781–5792.
27. Camidge DR, Barlesi F, Goldman JW, et al. Phase Ib study of telisotuzumab vedotin in combination with erlotinib in patients with c-Met protein-expressing non-small-cell lung cancer. *J Clin Oncol* 2023; 41: 1105–1115.
28. Camidge DR, Barlesi F, Goldman JW, et al. Telisotuzumab vedotin (Teliso-V) monotherapy in patients (pts) with previously treated c-Met–overexpressing (OE) advanced non-small cell lung cancer (NSCLC). *American Society of Clinical Oncology (ASCO) Abstract 9016* 2022.
29. Tan E-H, Lim W-T, Ahn M-J, et al. Phase 1b trial of ficlatuzumab, a humanized hepatocyte growth factor inhibitory monoclonal antibody, in combination with gefitinib in asian patients with NSCLC. *Clin Pharmacol Drug Dev* 2018; 7: 532–542.
30. Mok TSK, Geater SL, Su W-C, et al. A randomized phase 2 study comparing the combination of ficlatuzumab and gefitinib with gefitinib alone in Asian patients with advanced stage pulmonary adenocarcinoma. *J Thorac Oncol* 2016; 11: 1736–1744.
31. Spigel DR, Edelman MJ, O'Byrne K, et al. Results from the phase III randomized trial of

onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIB or IV non-small-cell lung cancer: METLung. *J Clin Oncol* 2017; 35: 412–420.

32. Guo R, Berry LD, Aisner DL, et al. MET IHC is a poor screen for MET amplification or MET Exon 14 mutations in lung adenocarcinomas: data from a tri-institutional cohort of the lung cancer mutation consortium. *J Thorac Oncol* 2019; 14: 1666–16671.
33. Awad MM, Oxnard GR, Jackman DM, et al. MET Exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. *J Clin Oncol* 2016; 34: 721–730.
34. Cappuzzo F, Marchetti A, Skokan M, et al. Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. *J Clin Oncol* 2009; 27: 1667–1674.
35. Yin X, Zhang T, Su X, et al. Relationships between Chromosome 7 Gain, MET Gene Copy Number Increase and MET Protein Overexpression in Chinese Papillary Renal Cell Carcinoma Patients. *PLoS One* 2015; 10: e0143468.
36. Lee HE, Kim MA, Lee HS, et al. MET in gastric carcinomas: comparison between protein expression and gene copy number and impact on clinical outcome. *Br J Cancer* 2012; 107: 325–333.
37. Noonan SA, Berry L, Lu X, et al. Identifying the appropriate FISH criteria for defining MET copy number-driven lung adenocarcinoma through oncogene overlap analysis. *J Thorac Oncol* 2016; 11: 1293–1304.
38. Chinese Society of Pathology, Pathology Quality Control Center, Lung Cancer Group of Chinese Medical Association Chinese Society of Oncology, China Anti-cancer Association Chinese Society of Lung Cancer, Chinese Thoracic Oncology Group. [Chinese expert consensus on clinical practice of MET detection in non-small cell lung cancer]. *Zhonghua Bing Li Xue Za Zhi* 2022; 51: 1094–103.
39. Camidge DR, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). *JCO* 2014; 32: 8001–8001.
40. Camidge DR, Otterson GA, Clark JW, et al. Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): updated safety and efficacy findings from a phase 1 trial. *JCO* 2018; 36: 9062–9062.
41. Wolf J, Seto T, Han J-Y, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med* 2020; 383: 944–957.
42. Schuler MH, Berardi R, Lim W-T, et al. Phase (Ph) I study of the safety and efficacy of the cMET inhibitor capmatinib (INC280) in patients (pts) with advanced cMET+ non-small cell lung cancer (NSCLC). *JCO* 2016; 34: 9067–9067.
43. Network NCC. NCCN Clinical Practice Guidelines in Oncology – Non-Small Cell Lung Cancer (Version 4.2024) 2024.
44. Garber K. MET inhibitors start on road to recovery. *Nat Rev Drug Discov* 2014; 13: 563–565.
45. Paik PK, Drilon A, Fan P-D, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer Discov* 2015; 5: 842–849.
46. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med* 2020; 26: 47–51.
47. Jamme P, Fernandes M, Copin M-C, et al. Alterations in the PI3K pathway drive resistance to MET inhibitors in NSCLC harboring MET exon 14 skipping mutations. *J Thorac Oncol* 2020; 15: 741–751.
48. Heist RS, Sequist LV, Borger D, et al. Acquired resistance to crizotinib in NSCLC with MET exon 14 skipping. *J Thorac Oncol* 2016; 11: 1242–1245.
49. Li H, Chen Z, Chen N, et al. Applications of lung cancer organoids in precision medicine: from bench to bedside. *Cell Commun Signal* 2023; 21: 350.
50. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; 348: 124–128.
51. Wolf J, Souquet P-J, Goto K, et al. Improved survival outcomes in patients with MET-dysregulated advanced NSCLC treated with MET inhibitors: results of a multinational retrospective chart review. *Clin Lung Cancer* 2023: S1525-7304(23)00172-9.
52. Negrao MV, Skoulidis F, Montesion M, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. *J Immunother Cancer* 2021; 9: e002891.

53. Veglia F, Perego M and Gabrilovich D. Myeloid-derived suppressor cells coming of age. *Nat Immunol* 2018; 19: 108–119.

54. Zhang Y, Yang Q, Zeng X, et al. MET Amplification attenuates lung tumor response to immunotherapy by inhibiting STING. *Cancer Discov* 2021; 11: 2726–2737.

55. Hegde PS, Karanikas V and Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. *Clin Cancer Res* 2016; 22: 1865–1874.

56. Lo Presti E, Dieli F and Meraviglia S. Tumor-infiltrating γδ T lymphocytes: pathogenic role, clinical significance, and differential programing in the tumor microenvironment. *Front Immunol* 2014; 5: 607.

57. Yoshimura K, Inoue Y, Tsuchiya K, et al. Elucidation of the relationships of MET protein expression and gene copy number status with PD-L1 expression and the immune microenvironment in non-small cell lung cancer. *Lung Cancer* 2020; 141: 21–31.

58. Pan Y, Yu Y, Wang X, et al. Tumor-associated macrophages in tumor immunity. *Front Immunol* 2020; 11: 583084.

59. Jackute J, Zemaitis M, Pranys D, et al. Distribution of M1 and M2 macrophages in tumor islets and stroma in relation to prognosis of non-small cell lung cancer. *BMC Immunol* 2018; 19: 3.

60. Sumitomo R, Hirai T, Fujita M, et al. M2 tumor-associated macrophages promote tumor progression in non-small-cell lung cancer. *Exp Ther Med* 2019; 18: 4490–4498.

61. Nishikoba N, Kumagai K, Kanmura S, et al. HGF-MET Signaling shifts M1 macrophages toward an M2-like phenotype through PI3K-mediated induction of arginase-1 expression. *Front Immunol* 2020; 11: 2135.

62. Kumar V, Donthireddy L, Marvel D, et al. Cancer-associated fibroblasts neutralize the anti-tumor effect of CSF1 receptor blockade by inducing PMN-MDSC infiltration of tumors. *Cancer Cell* 2017; 32: 654–668.e5.

63. Palle J, Hirsch L, Lapeyre-Prost A, et al. Targeting HGF/c-Met axis decreases circulating regulatory T cells accumulation in gastric cancer patients. *Cancers (Basel)* 2021; 13: 5562.

64. Sakaguchi S, Wing K, Onishi Y, et al. Regulatory T cells: how do they suppress immune responses? *Int Immunol* 2009; 21: 1105–1111.

65. Gordon S and Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity* 2010; 32: 593–604.

66. Gaggero S, Witt K, Carlsten M, et al. Cytokines orchestrating the natural killer-myeloid cell crosstalk in the tumor microenvironment: implications for natural killer cell-based cancer immunotherapy. *Front Immunol* 2020; 11: 621225.

67. Schoenfeld AJ, Rizvi H, Bandlamudi C, et al. Clinical and molecular correlates of PD-L1 expression in patients with lung adenocarcinomas. *Ann Oncol* 2020; 31: 599–608.

68. Peng S, Wang R, Zhang X, et al. EGFR-TKI resistance promotes immune escape in lung cancer via increased PD-L1 expression. *Mol Cancer* 2019; 18: 165.

69. Sabari JK, Leonardi GC, Shu CA, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. *Ann Oncol* 2018; 29: 2085–2091.

70. Gordon SR, Maute RL, Dulken BW, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. *Nature* 2017; 545: 495–499.

71. Mondal P, Kaur B, Natesh J, et al. The emerging role of miRNA in the perturbation of tumor immune microenvironment in chemoresistance: therapeutic implications. *Semin Cell Dev Biol* 2022; 124: 99–113.

72. Qureshi OS, Zheng Y, Nakamura K, et al. Trans-endocytosis of CD80 and CD86: a molecular basis for the cell-extrinsic function of CTLA-4. *Science* 2011; 332: 600–603.

73. J K, J H, J L, S FL and Yh K. Recent advances in tumor microenvironment-targeted nanomedicine delivery approaches to overcome limitations of immune checkpoint blockade-based immunotherapy. *J Control Release* 2021; 332: 109–126.

74. Sugiyama D, Hinohara K and Nishikawa H. Significance of regulatory T cells in cancer immunology and immunotherapy. *Exp Dermatol* 2023; 32: 256–263.

75. Bronte V, Brandau S, Chen S-H, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat Commun* 2016; 7: 12150.

76. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; 378: 2078–2092.

77. Otano I, Ucero AC, Zugazagoitia J, et al. At the crossroads of immunotherapy for oncogene-addicted subsets of NSCLC. *Nat Rev Clin Oncol* 2023; 20: 143–159.

78. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* 2019; 30: 1321–1328.

79. Reis H, Metzenmacher M, Goetz M, et al. MET expression in advanced non-small-cell lung cancer: effect on clinical outcomes of chemotherapy, targeted therapy, and immunotherapy. *Clin Lung Cancer* 2018; 19: e441–e463.

80. Guisier F, Dubos-Arvis C, Viñas F, et al. Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC With BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J Thorac Oncol* 2020; 15: 628–636.

81. Guisier F, Descourt R, Babey H, et al. Brief report: first-line pembrolizumab in metastatic non-small cell lung cancer habouring MET Exon 14 skipping mutation and PD-L1 ⩾50% (GFPC 01-20 Study). *Clin Lung Cancer* 2022; 23: e545–e549.

82. Gu L, Wei X, Zhang Z, et al. Treatment response to immunotherapy after crizotinib resistance in a patient with pulmonary sarcomatoid carcinoma harboring MET Exon 14 skipping mutation: a case report. *Clin Med Insights Oncol* 2022; 16: 11795549211067185.

83. Blasi M, Jonas K, Lüders H, et al. First-line immunotherapy for lung cancer with MET exon 14 skipping and the relevance of TP53 mutations. *Eur J Cancer (Oxford, England : 1990)* 2024; 199: 113556.

84. Qin H, Yan H, Chen Y, et al. Clinical outcomes for immune checkpoint inhibitors plus chemotherapy in non-small-cell lung cancer patients with uncommon driver gene alterations. *BMC Cancer* 2024; 24: 952.

85. Glodde N, Bald T, van den Boorn-Konijnenberg D, et al. Reactive neutrophil responses dependent on the receptor tyrosine kinase c-MET limit cancer immunotherapy. *Immunity* 2017; 47: 789–802.e9.

86. Spigel DR, Reynolds C, Waterhouse D, et al. Phase 1/2 study of the safety and tolerability of nivolumab plus crizotinib for the first-line treatment of anaplastic lymphoma kinase translocation – positive advanced non-small cell lung cancer (CheckMate 370). *J Thorac Oncol* 2018; 13: 682–688.

87. Yang JC-H, Shepherd FA, Kim D-W, et al. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M-positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. *J Thorac Oncol* 2019; 14: 933–939.

88. Mok TSK, Cortinovis DL, Majem M, et al. Efficacy and safety of capmatinib plus pembrolizumab in treatment (tx)-naïve patients with advanced non–small cell lung cancer (NSCLC) with high tumor PD-L1 expression: results of a randomized, open-label, multicenter, phase 2 study. *JCO* 2022; 40: 9118–9118.

89. Okajima D, Yasuda S, Maejima T, et al. Datopotamab deruxtecan, a Novel TROP2-directed antibody-drug conjugate, demonstrates potent antitumor activity by efficient drug delivery to tumor cells. *Mol Cancer Ther* 2021; 20: 2329–2340.

90. Goto Y, Su W-C, Levy BP, et al. TROPION-Lung02: Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) in advanced non-small cell lung cancer (aNSCLC). *JCO* 2023; 41: 9004–9004.

91. Borghaei H, Waqar SN, Bruno DS, et al. TROPION-Lung04: Phase 1b, multicenter study of datopotamab deruxtecan (Dato-DXd) in combination with immunotherapy ± carboplatin in advanced/metastatic non-small cell lung cancer (mNSCLC). *JCO* 2023; 41: TPS3158–TPS3158.

92. Levy BP, Reck M, Yang JC-H, et al. Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab in treatment-naive advanced/metastatic (adv/met) non–small cell lung cancer (NSCLC) with PD-L1 ⩾ 50% and without actionable genomic alterations. *JCO* 2022; 40: TPS3162–TPS3162.

93. Békés M, Langley DR and Crews CM. PROTAC targeted protein degraders: the past is prologue. *Nat Rev Drug Discov* 2022; 21: 181–200.

94. Li X and Song Y. Proteolysis-targeting chimera (PROTAC) for targeted protein degradation and cancer therapy. *J Hematol Oncol* 2020; 13: 50.

95. Dale B, Cheng M, Park K-S, et al. Advancing targeted protein degradation for cancer therapy. *Nat Rev Cancer* 2021; 21: 638–654.

96. Bondeson DP, Smith BE, Burslem GM, et al. Lessons in PROTAC design from selective degradation with a promiscuous warhead. *Cell Chem Biol* 2018; 25: 78–87.e5.

97. Li P, Jia C, Fan Z, et al. Discovery of novel exceptionally potent and orally active c-MET PROTACs for the treatment of tumors with MET alterations. *Acta Pharm Sin B* 2023; 13: 2715–2735.

98. Zhao H-Y, Xin M and Zhang S-Q. Progress of small molecules for targeted protein degradation: PROTACs and other technologies. *Drug Dev Res* 2023; 84: 337–394.

99. Jaynes JM, Sable R, Ronzetti M, et al. Mannose receptor (CD206) activation in tumor-associated macrophages enhances adaptive and innate antitumor immune responses. *Sci Transl Med* 2020; 12: eaax6337.

100. Zhou Y, Fei M, Zhang G, et al. Blockade of the phagocytic receptor MerTK on tumor-associated macrophages enhances P2X7R-dependent sting activation by tumor-derived cGAMP. *Immunity* 2020; 52: 357–373.e9.

101. Granhøj JS, Witness Præst Jensen A, Presti M, et al. Tumor-infiltrating lymphocytes for adoptive cell therapy: recent advances, challenges, and future directions. *Expert Opin Biol Ther* 2022; 22: 627–641.

102. Caushi JX, Zhang J, Ji Z, et al. Transcriptional programs of neoantigen-specific TIL in anti-PD-1-treated lung cancers. *Nature* 2021; 596: 126–132.

103. Galvano A, Gristina V, Malapelle U, et al. The prognostic impact of tumor mutational burden (TMB) in the first-line management of advanced non-oncogene addicted non-small-cell lung cancer (NSCLC): a systematic review and meta-analysis of randomized controlled trials. *ESMO Open* 2021; 6: 100124.

104. Min J, Long C, Zhang L, et al. c-Met specific CAR-T cells as a targeted therapy for non-small cell lung cancer cell A549. *Bioengineered* 2022; 13: 9216–9232.

105. Houot R, Schultz LM, Marabelle A, et al. T-cell-based Immunotherapy: adoptive cell transfer and checkpoint inhibition. *Cancer Immunol Res* 2015; 3: 1115–1122.

106. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med* 2020; 382: 545–553.

107. Bald T, Krummel MF, Smyth MJ, et al. The NK cell-cancer cycle – advances and new challenges in NK cell-based immunotherapies. *Nat Immunol* 2020; 21: 835–847.

108. Dudley JC, Lin M-T, Le DT, et al. Microsatellite instability as a biomarker for PD-1 blockade. *Clin Cancer Res* 2016; 22: 813–820.

109. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; 357: 409–413. https://doi.org/10.1126/science.aan6733.

110. Luchini C, Bibeau F, Ligtenberg MJL, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. *Ann Oncol* 2019; 30: 1232–1243.

111. Lan B, Ma C, Zhang C, et al. Association between PD-L1 expression and driver gene status in non-small-cell lung cancer: a meta-analysis. *Oncotarget* 2018; 9: 7684–7699.

112. Palmer C, Diehn M, Alizadeh AA, et al. Cell-type specific gene expression profiles of leukocytes in human peripheral blood. *BMC Genom* 2006; 7: 115.

113. Greenplate AR, Johnson DB, Ferrell PB, et al. Systems immune monitoring in cancer therapy. *Eur J Cancer* 2016; 61: 77–84.

114. Singal G, Miller PG, Agarwala V, et al. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non-small cell lung cancer using a clinicogenomic database. *JAMA* 2019; 321: 1391–1399. https://doi.org/10.1001/jama.2019.3241.

115. Bar J, Cai MH, Choi YC, et al. Prevalence, molecular characterization, and prognosis of MET–overexpressing non-small cell lung cancer (NSCLC) in a real-world patient cohort. *ESMO Congress* 2023: 1397P.

116. Lu S, Fang J, Li X, et al. Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study. *Lancet Respir Med* 2021; 9: 1154–1164.

117. Paik PK, Felip E, Veillon R, et al. Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. *N Engl J Med* 2020; 383: 931–943.

118. Yu Y, Zhou J, Li X, et al. Gumarontinib in patients with non-small-cell lung cancer harbouring MET exon 14 skipping mutations: a multicentre, single-arm, open-label, phase 1b/2 trial. *eClinicalMedicine* 2023; 59: 101952.