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CONSENSUS

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Expert consensus on the diagnosis and treatment of non-small cell lung cancer with MET alteration

Huijing Feng[1]*, Yang Xia[2]*, Wenxian Wang[3]*, Chunwei Xu[4,5]*, Qian Wang[6]*, Zhengbo Song[3], Ziming Li[7], Jinpu Yu[8], Wenzhao Zhong[9], Zhijie Wang[10], Yongchang Zhang[11], Jingjing Liu[12], Shirong Zhang[13], Xiuyu Cai[14], Anwen Liu[15], Wen Li[2], Ping Zhan[5], Hongbing Liu[5], Tangfeng Lyu[5], Liyun Miao[16], Lingfeng Min[17], Gen Lin[18], Long Huang[15], Jingping Yuan[19], Zhansheng Jiang[20], Xingxiang Pu[21], Chuangzhou Rao[22], Dongqing Lyu[23], Zongyang Yu[24], Xiaoyan Li[25], Chuanhao Tang[26], Chengzhi Zhou[27], Qi Mei[1], Hui Guo[28], Qian Chu[29], Rui Meng[30], Xuewen Liu[31], Jingxun Wu[32], Jin Zhou[33], Zhengfei Zhu[34], Weiwei Pan[35], Fei Pang[36], Meizhen Hu[36], Kai Wang[36], Fan Wu[37], Bingwei Xu[38], Ling Xu[39], Liping Wang[40], Youcai Zhu[41], Jisheng Li[42], Yanru Xie[43], Xinqing Lin[27], Jing Cai[15], Lin Wang[44], Yingying Du[45], Wang Yao[46], Xuefei Shi[47], Xiaomin Niu[7], Dongmei Yuan[5], Yanwen Yao[5], Jing Kang[9], Jiatao Zhang[9], Chao Zhang[9], Wenbin Gao[48], Jianhui Huang[43], Yinbin Zhang[49], Pingli Sun[50], Hong Wang[51], Mingxiang Ye[5], Dong Wang[5], Zhaofeng Wang[5], Yue Hao[3], Zheng Wang[52], Bing Wan[53], Donglai Lyu[54], Xiaodong Jiao[55], Lin Shi[56], Gang Lan[41], Shengjie Yang[57], Yanhong Shang[58], Yina Wang[59], Bihui Li[60], Gang Jin[61], Kang Zheng[62], Jun Ma[63], Wenfeng Li[64], Zhang Zhang[65], Zhongwu Li[66], Yuan Li[67], Zhefeng Liu[51], Xuelei Ma[68], Nong Yang[11], Lin Wu[21], Qiming Wang[69], Guansong Wang[70], Zhuan Hong[71], Jiandong Wang[72], Meiyu Fang[3], Yong Fang[73], Xixu Zhu[52], Yi Shen[74], Ke Wang[75,76], Xiubao Ren[77], Yiping Zhang[3], Shenglin Ma[78], Junping Zhang[1]*, Yong Song[5]*, Wenfeng Fang[79]*, Yuanzhi Lu[80]*

[1]Department of Thoracic Oncology, Shanxi Academy of Medical Sciences, Shanxi Bethune Hospital, Taiyuan 030032, China; [2]Key Laboratory of Respiratory Disease of Zhejiang Province, Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Zhejiang University School of Medicine, Cancer Center, Zhejiang University, Hangzhou 310009, China; [3]Department of Chemotherapy, Chinese Academy of Sciences University Cancer Hospital (Zhejiang Cancer Hospital), Hangzhou 310022, China; [4]Institute of Cancer and Basic Medicine (ICBM), Chinese Academy of Sciences, Hangzhou 310022, China; [5]Department of Respiratory Medicine, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China; [6]Department of Respiratory Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing 210029, China; [7]Department of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [8]Department of Cancer Molecular Diagnostics Core, Tianjin Medical University Cancer Institute & Hospital, Tianjin 300060, China; [9]Guangdong Lung Cancer Institute, Guangdong Provincial Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, School of Medicine, Guangzhou 510080, China; [10]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China; [11]Department of Medical Oncology, Lung Cancer and Gastrointestinal Unit, Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410013, China; [12]Department of Thoracic Cancer, Jilin Cancer Hospital, Changchun 130012, China; [13]Translational Medicine Research Center, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People's Hospital, Cancer Center, Zhejiang University School of Medicine, Hangzhou 310006, China; [14]Department of VIP Inpatient, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China; [15]Department of Oncology, Second Affiliated Hospital of Nanchang University, Nanchang 330006, China; [16]Department of Respiratory Medicine, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing 210008, China; [17]Department of Respiratory Medicine, Clinical Medical School of Yangzhou University, Subei People's Hospital of Jiangsu Province, Yangzhou 225001, China; [18]Department of Medical Oncology, Fujian Medical University Cancer Hospital & Fujian Cancer Hospital, Fuzhou 350014, China; [19]Department of Pathology, Renmin Hospital of Wuhan University, Wuhan 430060, China; [20]Department of Integrative Oncology, Tianjin Medical University Cancer Institute & Hospital, Tianjin 300060, China; [21]Department of Medical Oncology, Lung Cancer and Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410013, China; [22]Department of Radiotherapy and Chemotherapy, Hwamei Hospital, University of Chinese Academy of Sciences, Ningbo 315010, China; [23]Department of Pulmonary Medicine, Taizhou Hospital

of Wenzhou Medical University, Taizhou 317000, China; [24]Department of Respiratory Medicine, the 900th Hospital of the Joint Logistics Team (the Former Fuzhou General Hospital), Fujian Medical University, Fuzhou 350025, China; [25]Department of Oncology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100700, China; [26]Department of Medical Oncology, Peking University International Hospital, Beijing 102206, China; [27]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease; Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510300, China; [28]Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China; [29]Department of Oncology, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; [30]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China; [31]Department of Oncology, the Third Xiangya Hospital, Central South University, Changsha 410013, China; [32]Department of Medical Oncology, the First Affiliated Hospital of Medicine, Xiamen University, Xiamen 361003, China; [33]Department of Medical Oncology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu 610041, China; [34]Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China; [35]Department of Cell Biology, College of Medicine, Jiaxing University, Jiaxing 314001, China; [36]Shanghai OrigiMed Co, Ltd, Shanghai 201114, China; [37]Menarini Silicon Biosystems SpA, Shanghai 200333, China; [38]Department of Biotherapy, Cancer Institute, First Affiliated Hospital of China Medical University, Shenyang 110001, China; [39]Department of Interventional Pulmonary Diseases, Anhui Chest Hospital, Hefei 230011, China; [40]Department of Oncology, Baotou Cancer Hospital, Baotou 014000, China; [41]Department of Thoracic Disease Diagnosis and Treatment Center, Zhejiang Rongjun Hospital, The Third Affiliated Hospital of Jiaxing University, Jiaxing 314000, China; [42]Department of Medical Oncology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan 250012, China; [43]Department of Oncology, Lishui Municipal Central Hospital, Lishui 323000, China; [44]Department of Pathology, Shanxi Academy of Medical Sciences, Shanxi Bethune Hospital, Taiyuan 030032, China; [45]Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China; [46]Department of Interventional Oncology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510060, China; [47]Department of Respiratory Medicine, Huzhou Hospital, Zhejiang University School of Medicine, Huzhou 313000, China; [48]Department of Oncology, The Third Affiliated Hospital of Shenzhen University, Shenzhen 518001, China; [49]Department of Oncology, the Second Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an 710004, China; [50]Department of Pathology, The Second Hospital of Jilin University, Changchun 130041, China; [51]Senior Department of Oncology, The 5th Medical Center of Chinese PLA General Hospital, Beijing 100071, China; [52]Department of Radiation Oncology, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China; [53]Department of Respiratory Medicine, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing 210002, China; [54]Department of Clinical Oncology, The 901 Hospital of Joint Logistics Support Force of People Liberation Army, Hefei 230031, China; [55]Department of Medical Oncology, Shanghai Changzheng Hospital, Naval Medical University, Shanghai 200070, China; [56]Department of Respiratory Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China; [57]Department of Thoracic Surgery, Chuxiong Yi Autonomous Prefecture People's Hospital, Chuxiong 675000, China; [58]Department of Medical Oncology, Affiliated Hospital of Hebei University, Baoding 071000, China; [59]Department of Oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310000, China; [60]Department of Oncology, The Second Affiliated Hospital of Guilin Medical University, Guilin 541199, China; [61]Department of Oncology, The Second Hospital of Shanxi Medical University, Taiyuan 030001, China; [62]Department of Thoracic Surgery, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan 030013, China; [63]Department of Thoracic Surgery, Shanxi Provincial People's Hospital/The Fifth Hospital of Shanxi Medical University/ The Fifth Clinical Medical College of Shanxi Medical University, Taiyuan 030012, China; [64]Department of Radiation Oncology, First Affiliated Hospital of Wenzhou Medical College, Wenzhou 325000, China; [65]International Cooperative Laboratory of Traditional Chinese Medicine Modernization and Innovative Drug Discovery of Chinese Ministry of Education (MOE), Guangzhou City Key Laboratory of Precision Chemical Drug Development, School of Pharmacy, Jinan University, Guangzhou 510632, China; [66]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Pathology, Peking University Cancer Hospital & Institute, Beijing 100142, China; [67]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai 200032, China; [68]Department of Biotherapy, State Key Laboratory of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China; [69]Department of Internal Medicine, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou 450008, China; [70]Institute of Respiratory Diseases, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, China; [71]Department of Medical Oncology, Jiangsu Cancer Hospital, Nanjing Medical University Affiliated Cancer Hospital, Nanjing 210029, China; [72]Department of Pathology, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China; [73]Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou 310016, China; [74]Department of Thoracic Surgery,

Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China; [75]National Health Commission (NHC) Key Laboratory of Nuclear Medicine, Jiangsu Key Laboratory of Molecular Nuclear Medicine, Jiangsu Institute of Nuclear Medicine, Wuxi 214063, China; [76]Department of Radiopharmaceuticals, School of Pharmacy, Nanjing Medical University, Nanjing 210000, China; [77]Department of Immunology, Tianjin Medical University Cancer Institute & Hospital, Tianjin 300060, China; [78]Department of Oncology, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou Cancer Hospital, Cancer Center, Zhejiang University School of Medicine, Hangzhou 310006, China; [79]Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China; [80]Department of Clinical Pathology, The First Affiliated Hospital of Jinan University, Guangzhou 510630, China

ABSTRACT Alterations in the mesenchymal-epithelial transition factor (*MET*) gene are critical drivers of non-small cell lung cancer (NSCLC). In recent years advances in precision therapies targeting MET alterations have significantly expanded treatment options for NSCLC patients. These alterations include *MET* exon 14 skipping mutations (*MET* exon 14 skipping), *MET* gene amplifications, *MET* point mutations (primarily kinase domain mutations), and MET protein overexpression. Accurate identification of these alterations and appropriate selection of patient populations and targeted therapies are essential for improving clinical outcomes. The East China Lung Cancer Group, Youth Committee (ECLUNG YOUNG, Yangtze River Delta Lung Cancer Cooperation Group) has synthesized insights from China's innovative drug development landscape and clinical practice to formulate an expert consensus on the diagnosis and treatment of NSCLC patients with MET alterations. This consensus addresses key areas, such as optimal testing timing, testing methods, testing strategies, quality control measures, and treatment approaches. By offering standardized recommendations, this guidance aims to streamline diagnostic and therapeutic processes and enhance clinical decision-making for NSCLC with MET alterations.

KEYWORDS Mesenchymal-epithelial transition factor; *MET* exon 14 skipping mutation; *MET* amplification; non-small cell lung cancer; precision medicine; targeted therapy; tyrosine kinase

Introduction

Lung cancer remains one of the most prevalent malignancies in China and worldwide. Lung cancer has the highest incidence and mortality rates among all malignant tumors in China[1,2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and has an overall 5-year survival rate < 20%. In recent years, advances in understanding the molecular pathways driving cancer, especially the identification of tumor driver genes, have revolutionized the treatment paradigm for NSCLC. Research into new targets, mechanisms, and treatment strategies has made steady progress, offering increasingly personalized therapeutic options for patients. Among these advances, the mesenchymal-epithelial transition (*MET*) gene has emerged as a key tumor driver in NSCLC and garnered significant attention. Targeted therapies against MET alterations, such as approved medications (savolitinib and bozitinib) and medications in clinical trials (ensartinib), have been developed. Notably, all these MET inhibitors were independently developed in China with the research and clinical data demonstrating the growing impact of Chinese innovative drugs on domestic and international stages.

MET alterations and the pathogenic mechanisms

The *MET* gene, a proto-oncogene located on chromosome 7q21-31, is also known as *c-MET*, *RCCP2*, *HGFR*, and *DFNB97*. Spanning approximately 125 kb, the *MET* gene contains 21 exons and 20 introns. The *MET* gene encodes the MET protein, a receptor tyrosine kinase (RTK), which interacts with its natural ligand, hepatocyte growth factor (HGF). Upon HGF binding, MET dimerizes and undergoes

*These authors contributed equally to this work.
Correspondence to: Junping Zhang, Yong Song, Wenfeng Fang, and Yuanzhi Lu
E-mail: junpingzhang@yeah.net, Yong.song@nju.edu.cn, fangwf@sysucc.org.cn and yuanzhi.lu@jnu.edu.cn
ORCID ID: https://orcid.org/0009-0008-6325-5250, https://orcid.org/0000-0003-4979-4131, https://orcid.org/0000-0002-6440-8246 and https://orcid.org/0000-0003-2946-643X
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tyrosine phosphorylation, activating downstream signaling pathways, such as PI3K-AKT, MAPK, PI3K-AKT, JAK-STAT, and Wnt/β-catenin. These pathways drive cellular proliferation, growth, migration, invasion, and angiogenesis, making the MET pathway pivotal in normal tissue development and tumor progression[3-5].

MET alterations include gene fusions (e.g., exon 14 skipping mutations), amplification, point mutations (primarily in the kinase domain), and MET protein overexpression. These alterations abnormally activate the MET signaling pathway, promoting tumor initiation and progression[3,4,6].

Additionally, the interaction between MET protein with other RTK signaling pathways contributes to resistance against various targeted therapies, including those targeting EGFR, VEGFR, ALK, ROS1, and RET.

MET fusions (including exon 14 skipping mutations) and pathogenic mechanisms

MET exon 14 skipping mutations, also known as *MET-MET* fusions, represent a distinct subtype of *MET* fusions. These mutations occur primarily in the branch site (a single nucleotide), the poly-pyrimidine tract (16 nucleotides), the splice acceptor site (2 nucleotides upstream), and the splice donor site (2 nucleotides downstream)[7].

During transcription, *MET* exon 14 skipping mutations affect conserved sequences at RNA splice donor or acceptor sites, resulting in improper splicing of exon 14. Consequently, the MET protein loses its juxtamembrane domain or exhibits alterations, such as deletions of the Y1003 amino acid site, which impairs ubiquitination, leading to increased protein stability, reduced degradation, and persistent activation of downstream signaling pathways[8]. These effects collectively promote tumor development[9].

Public data have shown that *MET* exon 14 skipping mutations are the most prevalent *MET* gene alterations among the Chinese lung cancer population (**Figure 1**)[10].

In the absence of MET inhibitors, these mutations are associated with high tumor aggressiveness, resistance to anticancer therapy, and a poor prognosis[11,12].

Table S1 shows the locations of *MET* exon 14 skipping mutations. In addition to *MET* exon 14 skipping mutations, numerous other *MET* fusion types exist, although the incidence is relatively low with novel *MET* fusions occurring in 0.26%–0.29% of patients[13,14]. Secondary resistant *MET* fusions, emerging after treatment with tyrosine kinase inhibitors (TKIs), can constitute up to 5% of the MET alterations, which includes amplifications, mutations, and fusions[15]. Several *MET* fusion partner genes have been identified in NSCLC[16], including KIF5B, STARD3NL, HLA-DRB1, UBE2H[17], SLC1A2, PTPRZ1, EPHB4, THAP5, TNPO3, and DST, often co-occurring with TP53 mutations[14]. Notably, *MET* fusion proteins retaining an intact kinase domain (excluding *MET* exon 14) are more prevalent with 85.7% (6/7) of such patients responding effectively to MET TKIs[14].

In 2017 Davies et al.[18] reported the first case involving the identification and treatment of a *MET* fusion in NSCLC. Using AMP-based next-generation sequencing (NGS) for fusion gene detection, Davies et al.[18] identified the *HLA-DRB1-MET* fusion, which had not been previously described. The patient demonstrated a significant response to crizotinib, a small molecule tyrosine kinase inhibitor targeting HGFR activity. This case highlighted the role of *MET* fusion genes as oncogenic drivers.

In November 2017 Cho et al.[19] reported the first case of a *MET* fusion-positive lung adenocarcinoma. Targeted NGS of the patient's specimen revealed a *KIF5B-MET* fusion gene. Treatment with the MET inhibitor crizotinib resulted in a significant and sustained anti-tumor response, indicating the

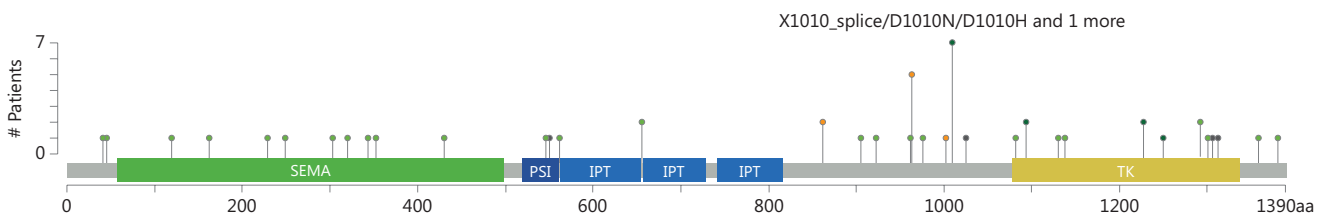


Figure 1 Frequency and location of *MET* hotspots in NSCLC. Schematic diagram of *MET* mutation hotspots and locations of lung cancer in Chinese population[10]. SEMA, semaphorin; PSI, plexin-semaphorin-integrin domain; IPT, immunoglobulin-plexins-transcription domain; TK, tyrosine kinase domain.

oncogenic potential of the *KIF5B-MET* fusion gene in lung adenocarcinoma.

In March 2018 Plenker et al.[20] published a study highlighting the clinical implications of *MET* structural alterations. Using hybrid-capture-based NGS Plenker et al.[20] analyzed specimens from two lung adenocarcinoma patients who tested negative for common lung cancer driver mutations. Two *MET* fusion transcripts were identified: the previously documented *KIF5B-MET* fusion; and a novel *STARD3NL-MET* fusion. The clinical response to crizotinib was assessed in both patients and a partial response was observed. Further functional studies in cellular models confirmed that crizotinib effectively inhibited MET, ALK among other kinases. These findings underscore the oncogenic role of *MET* structural alterations and the potential of *MET* structural alterations as actionable drug targets in lung cancer.

Wang et al.[21] presented epidemiologic data on *MET* fusion genes in NSCLC among the Chinese population at the 2018 ASCO Annual Meeting. Among 2410 NSCLC specimens analyzed, a novel *MET-ATXN7L1* fusion was identified in 1 patient (0.04%) with lung adenocarcinoma. This patient exhibited a partial response to crizotinib[16,21].

In 2018 Zhu et al.[17] reported the first case of a lung adenocarcinoma patient harboring a *MET-UBE2H* fusion in the *Journal of Thoracic Oncology*. This *MET-UBE2H* fusion was identified as a resistance mechanism to EGFR TKIs. The patient demonstrated a significant and sustained anti-tumor response to crizotinib and achieved a prolonged partial remission. The *MET-UBE2H* fusion is considered a novel rearrangement that confers resistance to EGFR TKIs[17].

Various *MET* fusion genes have been identified, including *SLC1A2-MET, PTPRZ1-MET, KIF5B-MET, HLA-DRB1-MET, SPECC1L-MET, CAPZA2-MET, CD47-MET, TES-MET, CAV1-MET, ITGA9-MET, TFEC-MET, CTTNBP2-MET, ANK1-MET, SPECC1L-MET, CAV1-MET*, and *STARD3NL-MET* (**Table S2**).

MET point mutations and the pathogenic mechanisms

MET point mutations occur in various regions of the gene, including the SEMA domain responsible for ligand binding, the juxtamembrane domain, and the kinase domain. In NSCLC clinically relevant *MET* mutations are predominantly concentrated in the kinase domain.

The known *MET* secondary mutation sites include V1003F, H1094Y, D1228A, D1228E, D1228G, D1228H, D1228N, D1228Y, D1228V, Y1230C, Y1230D, Y1230S, Y1230H, Y1230N, D1231Y, G1163R, G1090S, V1092L, V10921, L1195V, D1246N, and Y1248H, among others[22] (**Table S3**).

Some kinase domain mutations, such as D1228N, M1250T, and H1094Y/L, exhibit resistance to type I MET inhibitors (e.g., crizotinib) and have limited preclinical sensitivity data for type II MET inhibitors, such as cabozantinib and volitinib[23]. These mutations often contribute to acquired resistance. For example, Y1230C/H and D1228H/N, which are located in *MET* exon 14, mediate resistance following crizotinib therapy[24-28]. In addition, the D1246H mutation has been detected in plasma from an NSCLC patient with *MET* amplification who experienced disease progression after combination with EGFR-TKI/MET inhibitor therapy[29].

Point mutations in the SEMA domain (L229F, N375S, E168D, S323G) and juxtamembrane domain (R988C, R988C + T1010I, S1058P) have also been identified[30]. While the SEMA domain mutations have demonstrated oncogenic potential in cancers of unknown primary origin and renal cancer, their biological significance in lung cancer remains poorly understood[31,32].

MET amplification and its pathogenic mechanisms

MET gene amplification, which is characterized by an increase in the gene copy number (GCN), occurs in two forms (focal amplification and polysomy). Focal amplification involves an increase in the copy number of the *MET* gene or adjacent regions without a significant change in the copy number of other genes located on the same chromosome. Polysomy refers to the duplication of an entire chromosome, resulting in multiple copies of chromosome 7 within the cell. Both forms can lead to upregulation of *MET* mRNA levels and increased MET protein expression, which enhance activation of MET-related signaling pathways[11]. Amplification increases the number of MET receptors on the cell surface, leading to constitutive kinase activation[33,34].

MET gene amplification is associated with a higher histologic grade, advanced clinical stages, and poor prognosis. *MET* gene amplification can be classified into two types (primary and secondary amplifications).

Primary amplification occurs as a primary tumor driver gene alteration and is observed in 1%–5% of lung adenocarcinoma cases[11,33]. Low-level *MET* amplification often co-exists with other driver gene abnormalities (approximately 50%),

while high-level amplification typically occurs without other driver mutations. Targeted drug efficacy rates vary significantly, with 0% for low-level amplification or low MET protein expression and up to 67% for high-level amplification or high protein expression[35].

Having at least five copies of the *MET* gene renders tumor cells dependent on the signaling pathway[36]. In cases of high *MET* copy numbers, amplification serves as the primary oncogenic driver. Conversely, medium or low *MET* amplification levels are often accompanied by mutations in other oncogenic drivers, such as EGFR, RET, or BRAF[37]. These findings provide a theoretical basis for targeted therapy in patients with high-level *MET* amplification. Such patients demonstrate a better response to MET inhibitors, resulting in a higher tumor response rate[11].

Secondary *MET* amplification occurs after targeted therapy in NSCLC patients with other driver gene mutations, such as EGFR or ALK. When the EGFR or ALK signaling pathway is inhibited by an EGFR- or ALK-TKI, secondary *MET* amplification activates alternative signaling pathways, bypassing the inhibited pathway and triggering downstream activation. This mechanism contributes to resistance to TKIs. After an average of 9 months of treatment with first-, second-, or third-generation EGFR-TKIs, 15%–20% of patients develop *MET* amplification[33,38]. Similarly, *MET* amplification has been reported in ALK-rearranged NSCLC patients undergoing ALK-TKI treatment[39]. The INSIGHT 2 study, which was led by Wu[40], demonstrated that combining a highly selective MET inhibitor (tepotinib) with osimertinib is effective and safe for NSCLC patients with EGFR mutations and secondary *MET* amplification who have developed resistance to targeted therapy. This oral targeted therapy regimen has the potential to replace chemotherapy and warrants further investigation.

Currently, limited research exists on the differences in response to MET-TKI treatment between primary and secondary *MET* amplification. A retrospective clinical trial suggested that MET-TKIs are more effective in treating primary *MET* amplification compared to secondary amplification[41]. This finding contrasts with the previous understanding and may be explained by primary *MET* amplification functioning as an independent driver mutation. However, due to the small sample size and the lack of prospective study evidence, the clinical significance of this observation in guiding clinical treatment decisions requires further validation through larger and more reobust clinical studies.

MET-kinase domain duplication (KDD)

KDD refers to the duplication of the gene segment encoding a protein kinase domain, which results in a protein with multiple kinase domains from a single gene. KDDs have been identified in tumor types that potentially contribute to acquired resistance and show sensitivity to matched targeted therapies.

In a large-scale clinical sequencing study by Gay et al.[42], 114,200 patients with advanced tumors underwent CGP to test 184–406 tumor-related genes. Among these patients, 598 (0.62%) exhibited KDD with *MET*-KDD accounting for 3.18% (19/598). In 2019 the AACR reported the first data on *MET*-KDD in the Chinese lung cancer population; the incidence of *MET*-KDD was 0.09% (6/6837)[43].

Plenker et al.[20] reported a case of *MET*-KDD in a 60-year-old male diagnosed with ALK fusion-positive lung adenocarcinoma. After chemotherapy led to stable disease, treatment with ceritinib resulted in a partial response lasting 3 months before progression occurred. Subsequent NGS revealed a newly acquired *MET*-KDD, while the *ALK* fusion persisted. Treatment with crizotinib resulted in another partial response, which was sustained for 3 months.

MET overexpression and the pathogenic mechanisms

MET overexpression results from various *MET* gene alterations, such as *MET* amplification and exon 14 skipping mutations. These changes lead to overproduction or impaired degradation of the c-MET protein, leading to sustained abnormal activation of downstream pathways, such as HGF/MET. This process promotes increased cell proliferation, invasion, inhibition of apoptosis, and angiogenesis, driving tumor growth and metastasis.

It has been reported that MET protein overexpression occurs in 13.7%–63.7% of NSCLC cases[44-46]. Among EGFR-mutant advanced NSCLC patients treated with EGFR-TKIs, the incidence ranges from 30.4%–37.0%[45].

MET protein overexpression has been incorporated into the inclusion criteria for several clinical trials of MET inhibitors, such as INSIGHT, TATTON, and SAVANNAH, due to its significance as a biomarker[47-49].

The correlation between MET protein overexpression and other MET alterations is low between MET protein expression, as measured by IHC staining, and exon 14 skipping mutations[50-52].

The relationship between MET overexpression and *MET* amplification remains an area of active investigation. Data from the TATTON study revealed that 80% of patients who developed MET protein overexpression (≥ 50% of tumor cells with a 3+ score) after acquiring resistance to EGFR-TKIs also exhibited *MET* gene amplification (*MET* GCN ≥ 5 or *MET*/CEP7 > 2)[53]. In contrast, a study of 181 lung adenocarcinoma patients who had not received targeted therapy showed that only 1% of patients with MET protein overexpression (IHC score ≥ 200) had *MET* gene amplification[50]. Patients without *MET* amplification may still have MET overexpression and could potentially benefit combining EGFR TKIs and MET inhibitors based on clinical studies[47,49].

MET alteration testing methods

Various molecular analysis methods are available for detecting MET abnormalities in NSCLC, including immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), reverse transcription-quantitative polymerase chain reaction (RT-PCR), Sanger sequencing, and NGS. Each method has specific advantages and limitations, depending on the type of MET alteration, sample type and quality, tumor content, and laboratory conditions.

The National Comprehensive Cancer Network (NCCN) guidelines have emphasized the importance of MET testing in NSCLC. Since 2014 the NCCN has included *MET* amplification and mutations among the recommended biomarkers to guide treatment and encouraged participation in clinical trials targeting rare mutations. The *2024 NCCN NSCLC Guidelines* highlight *MET* exon 14 skipping as a critical molecular test, with a strong recommendation for treatment using highly selective MET inhibitors. In addition, testing for other resistance mechanisms, such as *MET* amplification, is advised to guide treatment decisions for patients resistant to EGFR-TKIs.

Detection of *MET* fusion (*MET* exon 14 skipping mutation)

Methods for detecting *MET* exon 14 skipping mutations[54-57] include Sanger sequencing, FISH, RT-PCR, and NGS. Among these methods, Sanger sequencing is less commonly used due to low sensitivity and throughput. FISH is limited in detecting complex or novel fusion types[58]. NGS is increasingly favored in clinical practice for the ability to detect a wide range of gene fusions. Given the diverse forms of *MET* exon 14 skipping mutations, special attention is needed in clinical testing and interpretation[59].

RT-PCR

RT-PCR detects *MET* exon 14 skipping mutations using RNA as the target. Primers are designed in the regions of *MET* exons 13 and 15 to amplify specific products, enabling accurate mutation detection[60]. However, this method may miss rare mutations with similar functional impacts, such as amino acid changes at the Y1003 site (accounting for approximately 2% of all positive cases[61]) or deletions[11]. For patients with borderline-positive results, careful interpretation is essential and should consider sample quality, tumor cell content, and test quality control metrics. If necessary, retesting on other platforms may be considered[59].

NGS

NGS offers significant advantages in detecting *MET* fusions, including the ability to identify all fusion genes and fusion gene partners, thereby overcoming the limitations of conventional methods, such as missed detections, misdetections, or the inability to identify fusion partners. NGS includes DNA- and RNA-based approaches. DNA-based NGS primarily detects mutations and common fusion partners. DNA-based NGS is limited in detecting rare fusion partners due to potential false positives and constraints in analyzing intronic regions. Currently, hybrid-capture-based NGS is the primary method used. In contrast, RNA-based NGS is specialized for detecting gene fusions, including rare fusion partners. The most commonly used methods are Anchored Multiplex PCR 61 (AMP[62]) technology or the improved version (PANO-Seq®).

Song et al.[63] demonstrated the effectiveness of RNA + DNA sequencing using NGS technology by combining the strengths of DNA-based mutation and RNA-based fusion detection for the first time in large-scale clinical testing. This approach detected 12%–16% of actionable targets in samples previously deemed negative by hybrid capture testing, including rare fusion targets, such as *NRG1, NTRK, MET*, and *EGFR* fusions, that might have been otherwise missed.

Given the diversity of variant sites and forms leading to *MET* exon 14 skipping mutations, as well as the high heterogeneity caused by alterations in *MET* exon 14, it is essential to select appropriate NGS platforms.

To ensure accurate detection of *MET* exon 14 skipping mutations using NGS, the bioinformatics analysis database

should encompass comprehensive and regularly updated information on mutation sites. Verification using RT-PCR or RNA sequencing is recommended for suspected *MET* exon 14 skipping mutations detected through NGS, guided by bioinformatics predictions. With sufficient optimization, DNA-based NGS platforms can achieve high sensitivity and specificity for detecting *MET* exon 14 skipping mutations. Liquid biopsy samples can be used for DNA-based NGS testing in cases in which tumor tissue or cytology samples are unavailable. However, certain limitations must be considered when using liquid biopsy samples. The relatively low concentration of ctDNA in patients may require highly sensitive detection methods, thereby increasing the risk of false-negatives. Furthermore, the effectiveness of ctDNA detection depends on the coverage of the detection probes, potentially limiting the accuracy for certain mutations. If a negative result is obtained from liquid biopsy testing, the possibility of a false-negative should be acknowledged.

Detection of *MET* mutations

MET mutations can be detected using traditional methods that target specific gene regions or NGS, which enables the simultaneous detection of multiple gene mutations and is ideal for comprehensive genomic analysis.

DNA-based hybrid capture NGS is the preferred method for detecting *MET* gene point mutations. This method uses a stable DNA template, ensuring complete coverage of all exon sequences in the *MET* gene and enabling accurate identification of missense mutations. Hybrid capture probes are specially designed to amplify genomic regions comprehensively, eliminate duplicate sequences, and reduce analytical noise. Moreover, targeted coverage of intronic regions can prevent primer binding issues while simultaneously detecting genomic variations within these regions. The hybrid capture approach, which spans the entire genome, also corrects sequencing biases and minimize allele dropout. This method also provides superior accuracy for detecting missense mutations[64].

Detection of *MET* amplification

The primary methods for detecting *MET* gene amplification are FISH and NGS. FISH is considered the gold standard for detecting *MET* amplification. However, the criteria for defining *MET* gene amplification and the clinical benefit threshold remain unclear.

The *MET* gene is located on chromosome 7 and trisomy or polysomy of chromosome 7 is a common pan-cancer genetic marker that can be misinterpreted as *MET* amplification[65]. FISH is particularly useful in distinguishing between these anomalies. In cases of chromosome 7 polysomy, the ratio of the *MET* gene-to-the centromere of chromosome 7 (*MET*/CEP7) remains unchanged. Converstly, a higher *MET*:CEP7 ratio indicates focal amplification of the *MET* gene.

FISH

FISH uses fluorescent probes to label the *MET* gene *in situ*, enabling direct observation of MET fluorescent signals in individual tumor cells under a microscope to calculate the *MET* gene copy number. FISH can also label the *MET* gene and CEP7 to determine the *MET*:CEP7 ratio in tumor cells.

Currently, no standardized interpretation guidelines exist for detecting *MET* amplification *via* FISH (**Figure 2**), but accurate patient stratification is crucial for effective MET-targeted therapies[66]. The primary criteria used in clinical practice are the University of Colorado Cancer Center (UCCC) and Cappuzzo criteria. The inclusion criteria typically include *MET* GCN ≥ 5 or *MET*/CEP7 ≥ 2 in clinical trials investigating *MET* gene amplification as a resistance mechanism to EGFR-TKIs[47,67]. A *post-hoc* subgroup analysis of a Ib/II trial combing capmatinib and gefitinib in NSCLC patients demonstrated that a *MET* GCN > 6 threshold, as detected by FISH, offered the best predictive performance for treatment efficacy[68]. A retrospective study categorized the *MET*:CEP7 ratio into the following three amplification levels: low (≥ 1.8 to ≤ 2.2); intermediate (> 2.2 to < 5); and high (≥ 5)[37]. However, the study evidence level was weaker than multicenter clinical trial findings. A phase I clinical study (NCT02896231) enrolled 17 advanced NSCLC patients with primary *MET* amplification, which was defined as a GCN ≥ 5 by FISH or a *MET* copy number ≥ 2.25 by NGS. Treatment with bozitinib yielded an objective response rate (ORR) of 41.2%[69], supporting the use of MET inhibitors in patients with *MET* GCN ≥ 5.

DNA-based NGS

NGS can determine *MET* gene copy number variations (CNVs) by assessing sequencing depth and mutation frequency at specific sites. NGS can also establish criteria to distinguish *MET* gene amplification from chromosome 7 polysomy by evaluating additional genes on chromosome 7, such as neighboring genes (LINC01510 and CAPZA2) with the sequencing depth

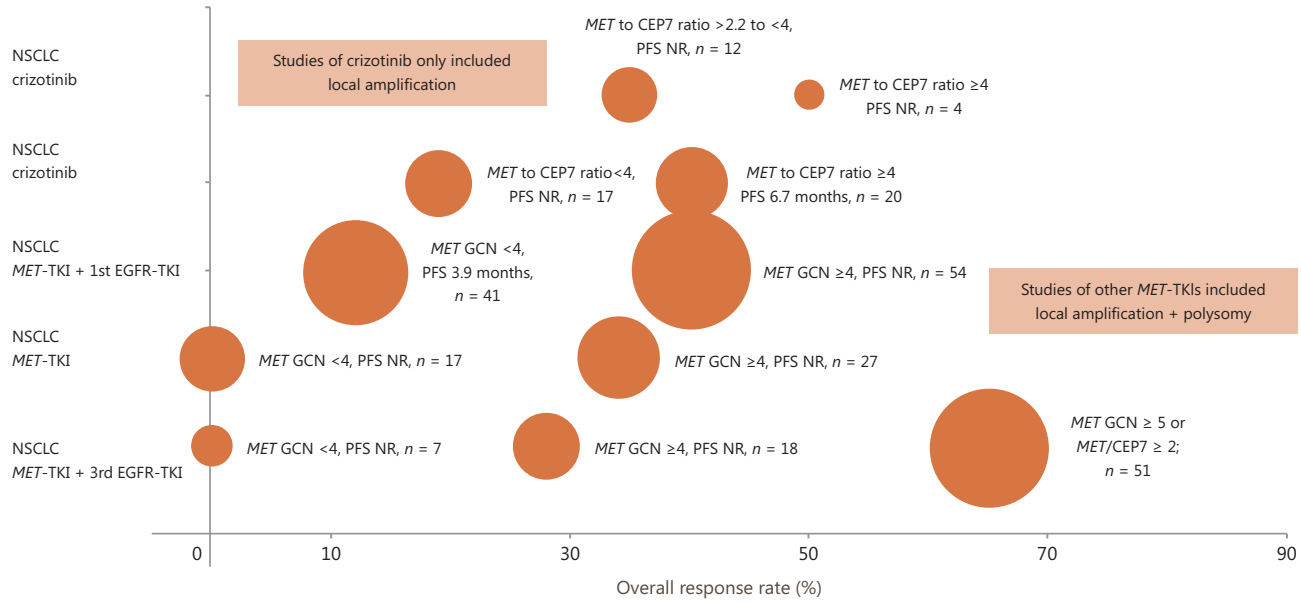


Figure 2 Judgment criteria of *MET* dual probe *in situ* hybridization testing.

and distribution characteristics of other chromosomes. This approach helps identify focal amplification and differentiate it from polysomy[11].

A precise threshold for *MET* amplification using NGS has not been standardized. Several NGS studies use *MET* GCN ≥ 5 as the threshold[70]. Other definitions include fold-changes > 1.6 or 3[71,72]. A prospective multi-cohort clinical study (GENOMETRY mono-1) set a higher threshold of 10[73].

A control test using a patient's normal samples, such as peripheral blood[74], is required for NGS testing. In addition to distinguishing between polysomy and focal amplification, NGS offers the advantage of simultaneously identifying other genomic alterations. CNVs detected by NGS may reflect changes caused by aneuploidy rather than focal amplification. Moreover, it is essential to perform cell purity and ploidy correction before reporting copy number variations to ensure accurate results.

Salido et al.[75] reported that NGS detected only 53.4% of the *MET* amplifications identified by FISH. This discrepancy can be attributed to two factors. First, NGS has difficulty detecting polysomy amplifications. Second, the sensitivity of NGS detection is influenced by the tumor purity and DNA content of the tissue. When the tumor DNA content is low, the accuracy of NGS detection decreases significantly. Therefore, NGS is suitable for initial patient screening and for patients with negative NGS results, FISH testing should be conducted to minimize the risk of missed detections.

Detection of *MET*-KDD

The main methods for detecting KDD in genes are discussed below.

NGS

NGS can be used to detect KDD[43] and offers detailed genome-level information and identification of duplication events that may impact gene function. Duplicated regions can be detected through whole-genome or targeted sequencing. Analysis of sequencing data allows for the identification of gene duplications or duplications of specific gene segments.

Comparative genomic profiling (CGP)

CGP is used to compare genomic characteristics across samples, enabling the detection of CNVs, gene mutations, and other genomic alterations. CGP is particularly useful for detecting KDD[42] because CGP can identify duplications, deletions, or rearrangements by analyzing CNVs within the genome.

Detection of MET overexpression

IHC is the method used to detect MET protein overexpression. This technique relies on specific antigen-antibody binding, in which a labeled antibody is conjugated to a chromogenic agent, such as a fluorophore, enzyme, metal ion, or isotope. Upon reaction, the chromogenic agent produces a color change, which enables the identification of antigens

(peptides and proteins) within tissue cells. This process allows for the localization, qualitative analysis, and relative quantification of the target proteins. Several antibodies used wordwide for MET detection have been approved as domestic medical device products in China involving various clone numbers. The staining performance of different antibodies varies and there is no standardized interpretation criterion (**Table 1**).

Current interpretation standards in clinical research combine the intensity of antibody expression with the percentage of tumor cells exhibiting that expression. In the TATTON and SAVANNAH studies, patients with MET IHC ≥ 50% strong tumor cell staining (3+) were enrolled using the SP44 antibody clone[67]. The INSIGHT study enrolled patients with moderate (2+) or strong (3+) staining in ≥ 50% of tumor cells using the D1C1 antibody clone[47]. The NCT01610336 study also enrolled patients with moderate (2+) or strong (3+) staining in ≥ 50% of tumor cells using the 3077 antibody clone[68]. Given the diversity of antibodies and the lack of standardized interpretation criteria, comparative studies are needed to assess consistency among different antibodies. Moreover, further clinical research is required to validate the clinical significance of MET protein overexpression and refine interpretation criteria and benefit thresholds. Clinical studies currently recommend that IHC testing results should include at least the information on the antibodies used, the percentage of positive tumor cells, and the staining intensity. Comparison of MET alteration testing methods and recommendation level in NSCLC is listed in **Table 2**.

Content requirements of MET testing report

A standardized genetic testing report should include essential information, such as patient demographics, sample pathology details, testing methods, reagents and systems used, quality control data, test results, variant classification and interpretation, clinical annotations, and any necessary remarks. The remarks section should address the limitations of the testing method, any special circumstances encountered during testing, and any additional work required. This consensus provides standardized recommendations for MET testing.

Reporting standards for *MET* exon 14 skipping mutation

The following should be included in DNA-based NGS reports: a clear description of the mutation (e.g., *MET* exon 14 skipping mutation); mutation site information; variant allele frequency; and reference transcript [commonly used *MET* gene transcripts are NM_000245 and NM_001127500 (attention should be given to the differences in sequence numbering between them)]. The report should clearly indicate whether the variation causes a *MET* exon 14 skipping mutation. If uncertain, whether the variation causes a *MET* exon 14 skipping mutation should be detailed in the variant interpretation section. The methods section should specify the coverage of *MET* exons and introns to enable physicians to fully assess the detection capability. For RNA-based tests, such as RT-PCR and RNA sequencing, the report should explicitly state if the mutation involves *MET* exon 14 skipping.

Reporting standards for MET gene amplification

The following should be included in FISH detection reports: the number of tumor cells assessed; the average *MET* copy number per cell; the average CEP7 copy number per cell;

Table 1 Interpretation criteria of MET overexpression testing

Study	Therapy	Population	Anti-METAb	Judgment criteria	Standards for positive
INSIGHT[47]	Tepotinib + gefitinib	Resistance to EGFR TKI	D1C1 Ab	Clinical scoring	≥ 50%tumor cells 2+ or 3+
TATTON[48]	Savolitinib + osimertinib	Resistance to EGFR TKI	SP44 Ab	Clinical scoring	≥ 50% tumor cells 3+
SAVANNAH	Savolitinib + osimertinib	Resistance to EGFR TKI	SP44 Ab	Clinical scoring	≥ 50% tumor cells 3+
NCT01610336[68]	Capmatinib + gefitinib	Resistance to EGFR TKI	3077	Clinical scoring	≥ 50% tumor cells 2+ or 3+
NCT03539536[76]	Teliso-V (MET ADC)	EGFR wt, MET+, second-line or above	SP44 Ab	Clinical scoring	Non-squamous cell carcinoma: ≥ 25% tumor cells 3+ squamous cell carcinoma: ≥ 75% tumor cells 1+
NCT02099058[77]	Teliso-V	Advanced solid tumors	SP44 Ab	H score	H-score ≥ 150

Table 2 Comparison of MET alteration testing methods and recommendation level in NSCLC

MET aberration	Detection technique	Tested material	Evaluation criteria	Advantages	Disadvantages
MET overexpression	IHC antibodies	FFPE slide	Semi-quantitative score 0–3+	Technique widely used and available, fast and cheap	Observer-dependent, tissue sectioning artefacts, new FFPE slide for every analysis, no consensus on scoring system and cut-off
MET exon 14 skipping	RNA NGS (amplicon-, AMP-, or hybridization-based)	RNA from FFPE or fresh frozen material	Mutation, coverage, MAF, fusion product of exons 13 and 15	Sensitive, reliable, direct detection of alternative splicing, multiplexing	RNA degradation, underlying mutation cannot be determined
	RT-PCR	RNA from FFPE or fresh frozen material	Fusion product of exons 13 and 15	Sensitive, reliable, direct detection of alternative splicing, fast turnaround time, widely used and available	RNA degradation, underlying mutation cannot be determined, targeted mutations only
MET point mutations	DNA NGS (amplicon- or hybridization-based)	DNA from FFPE, fresh frozen material, or liquid biopsy	Mutation, coverage, VAF	Sensitive, reliable, detection of exact mutation, multiplexing	No assessment of splicing effect
	Sanger sequencing	DNA from FFPE, fresh frozen material, or liquid biopsy	Mutation, VAF	Detection of exact mutation, fast turnaround time, widely used and available	Sensitivity, single assay for each target, no assessment of splicing effect
MET amplifications	FISH	FFPE slides	*MET* GCN, *MET*/CEN7 ratio	Technique widely used and available, detection of focal amplification, polysomy, and chromosome duplications	Observer-dependent, tissue sectioning artefacts, new FFPE slide for every analysis, no consensus on scoring system and cut-off
	DNA NGS (amplicon- or hybridization-based)	DNA from FFPE, fresh frozen material, or liquid biopsy	Mutation, coverage, VAF	Sensitive, DNA from FFPE easily accessible, multiplexing	High number of false negatives, no standardized cutoff or bioinformatics, no morphological correlation
	Other DNA-based technologies (ddPCR, NanoString nCounter technology)	DNA from FFPE, fresh frozen material, or liquid biopsy	Expression, GCN	DNA from FFPE easily accessible	High number of false-negatives, no morphologic correlation, no standardized cut-off, large amounts of DNA needed
MET fusions (excluding MET exon 14 skipping)	RNA NGS (AMP- or hybridization-based)	RNA from FFPE or fresh frozen material	Fusionreads, 3′-5′ imbalance	Sensitive, reliable detection of known and novel fusion partners, multiplexing	RNA degradation
	DNA NGS (Hybridization-based)	DNA from FFPE	Fusionreads, 3′-5′ imbalance, coverage,	DNA from FFPE easily accessible, detection of known and novel fusion partners if region is covered, multiplexing	False-negative results, novel fusions are problematic due to location of fusion break point
	FISH	FFPE slides	n.a. break-apart events	Technique widely used and available	No standardized assay available, observer-dependent, tissue sectioning artefacts, new FFPE slide for every analysis
	RT-PCR	RNA from FFPE	Fusion product	Technique widely used and available	No standardized assay available, only for known fusion partners, RNA degradation

[78]IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; FFPE, formalin-fixed paraffin-embedded; RT-PCR, quantitative real-time polymerase chain reaction; ddPCR, digital droplet PCR; n.a., not available; GCN, gene copy number; CEN7, centromere of chromosome 7; AMP, anchored multiplex polymerase chain reaction; NGS, next-generation sequencing; VAF, variant allele frequency.

the ratio of average *MET* copy number-to-average CEP7 copy number; and the proportion of tumor cells exhibiting amplification. The *MET* gene amplification status should be determined based on applicable criteria with a clear differentiation between focal amplification and polysomy when positive. The NGS report should provide a clear description of the variant information, gene copy number details, and the positive threshold for *MET* gene copy number variation, as determined by the testing platform. For NGS reports of *MET* gene amplification using liquid samples, the report should include details on the higher false-negative rate caused by low sensitivity of liquid biopsy, the positive thresholds specific to liquid biopsy, and any limitations of the method, in addition to the standard information provided.

Reporting standards for MET overexpression

The IHC report for *MET* testing should include the following: patient details (including name, gender, age, and outpatient/inpatient ID); name of the responsible physician; date of specimen submission; pathology report identification number; specimen collection site; specimen type; antibody information; detection method; whether image analysis was used; control settings; whether the sample size is sufficient for evaluation; and result interpretation (i.e., 0, 1+, 2+, or 3+).

MET testing procedure

Selecting an appropriate detection method for *MET* mutations in NSCLC in clinical practice requires consideration of multiple factors, including the target mutations, specimen type, the number and types of genes tested, detection costs, laboratory conditions, and reagent approvals. Multi-platform validation may be necessary to confirm results. Based on current evidence and clinical trials, the recommended workflow for MET testing is outlined in **Figure 3**.

Preferred specimens are tumor tissues or cytologic samples. Cytologic samples should contain > 200 tumor cells to ensure the reliability of the detection results. A DNA-based NGS platform that includes the *MET* gene should be used to detect various types of *MET* mutations. When DNA-based NGS results are negative, RNA-based NGS should be considered for additional testing. IHC technology can be used for preliminary screening of MET overexpression in tumor tissue

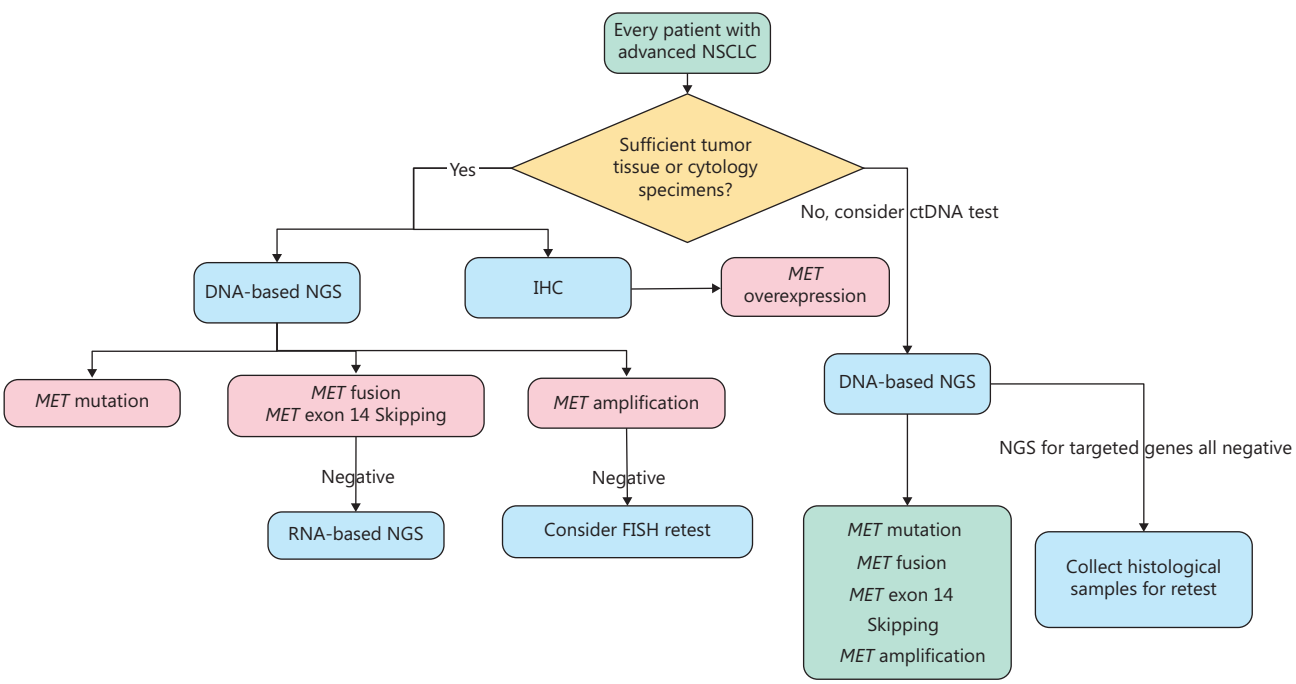


Figure 3 Strategy of MET testing in NSCLC.

or cytology samples. If tumor tissue or cytology specimens are unavailable, liquid biopsy samples can be used to detect various *MET* gene mutations.

To evaluate the effectiveness of inhibitors targeting *MET* mutations, it is essential to integrate the mutation profile and assess the presence of concurrent mutations, such as CDK4, MYC, or FGFR amplifications, which may affect drug resistance. Complex test results should be interpreted by a molecular tumor board (MTB) to ensure a thorough understanding, rather than focusing solely on *MET* mutations.

MET testing quality control

Sample selection and processing method

It is advisable to collect samples at one time to preserve tumor tissue specimens for molecular testing, which can meet the requirements for both pathologic and molecular diagnoses. NGS multi-gene testing is recommended for patients who develop treatment resistance and require furgher biopsies to detect genetic alterations or explore resistance mechanisms. This approach allows for comprehensive genetic information from limited specimens and reduces the need for additional invasive sampling and guiding subsequent treatment decisions.

All tissue and cytology specimens must undergo quality control by a pathologist to evaluate the tumor type, cell content, necrosis and hemorrhage rates, and stroma. It is necessary to select the appropriate type of histologic specimen for molecular testing and to ensure an adequate number of tumor cells for DNA or RNA extraction. If feasible, tumor enrichment procedures may also be performed to maximize tumor content in the specimen. After routine histologic diagnosis, sufficient tissue should be preserved for molecular biological testing to guide treatment based on molecular profiling[79,80]. Adequate tissue must be retained to allow for molecular profiling for advanced NSCLC[79-86].

The primary sample types for MET detection include tumor tissue, cytology samples, and body fluid samples. *MET* exon 14 skipping mutations can be detected using RNA and it is important to ensure timely fixation and appropriate storage to prevent RNA degradation. Formalin-fixed paraffin-embedded samples, cell blocks, and cell smears are acceptable for molecular testing, while acid-treated specimens should be avoided[82,87,88].

When selecting an appropriate testing method, laboratory conditions, sample type, sample quantity, and quality control results should be considered. Liquid biopsy samples can serve as a supplementary testing option when tumor tissue and cytology samples are unavailable and the limitations of using such samples must be clearly stated in the test report.

Tumor tissue samples

Tumor tissue samples include fresh tissue and formalin-fixed paraffin-embedded (FFPE) samples. FFPE samples, including surgical and biopsy samples, should be prioritized for testing. The tumor cell proportion must be evaluated before testing to ensure the requirements are met. It is recommended to select surgical samples with a higher proportion of tumor cells, aiming for a minimum tumor cell content of 20%[89]. FFPE samples should be processed according to established pathologic standards.

Cytology samples

Testing can be performed using cytology samples, such as sputum, bronchoalveolar lavage fluid, pleural or peritoneal effusions, or endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA) biopsies, for advanced lung cancer patients who cannot provide tumor tissue. A cellular assessment should be performed prior to testing or the samples should be prepared as paraffin-embedded specimens and tested once the necessary requirements are met.

Liquid biopsy samples

MET exon 14 skipping mutations may be assessed using blood testing for advanced NSCLC patients who cannot provide tissue or cytology samples. Circulating tumor DNA (ctDNA) extracted from the patient's plasma serves as a viable option for genetic testing. Cerebrospinal fluid (CSF) can be used to enrich ctDNA from intracranial tumors in advanced NSCLC patients with leptomeningeal metastases, making CSF a suitable option for relevant genetic testing. The ctDNA content in blood and CSF is significantly lower compared to tissue samples, leading to reduced sensitivity for mutation detection.

Internal and external quality control of MET testing

A robust quality control system is crucial for ensuring the reliability of pathologic diagnosis and the accuracy of MET testing in clinical practice. Laboratories should establish standard operating procedures (SOPs) and quality control systems.

Internal quality control

A standardized testing process must be established before testing and performance validation should be carried out. Positive and negative controls should be included during testing. All procedures should be performed by professionally trained personnel with designated individuals responsible for quality monitoring, regular training sessions, and data comparison analysis.

It is recommended to use laboratories certified by the College of American Pathologists (CAP), the Clinical Laboratory Improvement Amendments (CLIA), accredited by institutions, such as the Clinical Laboratory Management Regulations or the China National Accreditation Service for Conformity Assessment (CNAS), or institutions that meet relevant industry standards for molecular testing.

The testing method must use reagents and platform equipment officially approved by national authorities. Officially validated NGS platforms or RT-PCR multi-gene panels can be used to simultaneously detect mandatory and additional genes. During NGS experimental procedures, special attention should be given to avoid cross-contamination between different samples. For example, when using automated instruments, consider conducting library preparation for individual samples in sealed conditions to minimize the risk of cross-contamination.

External quality control

Laboratories should participate in annual quality control programs or inter-laboratory quality assessments, such as those organized by the Pathology Quality Control Center (PQCC), the CAP, or the CLIA, to ensure the accuracy of laboratory procedures and the validity of test results. The reliability of test results can also be determined by comparing the results with results from qualified laboratories using the same testing methods. For inconsistent results, alternative methods should be available for verification and review.

Enhance communication with clinical and pathology teams

MET alterations are inherently complex due to the diversity of variant sites and forms in *MET* exon 14 skipping mutations, the lack of unified standards for *MET* gene amplification and overexpression, and unclear thresholds for clinical interpretation. These challenges necessitate close communication among testing laboratories, clinical teams, and pathology departments to ensure effective coordination and information exchange.

Treatments for NSCLC patients with MET alterations

Capmatinib

Capmatinib is the first highly selective single-target MET inhibitor approved worldwide. It is administered at 400 mg BID under fasting conditions.

Capmatinib has shown good efficacy in both treatment-naïve and previously-treated NSCLC patients with *MET* exon 14 skipping mutation. Patients receiving capmatinib as a first-line treatment exhibit a higher ORR and disease control rate (DCR), as well as longer duration of response (DoR) and progression-free survival (PFS). Capmatinib approval was mainly based on results from a pivotal study for new drug registration (the prospective, non-randomized, open-label phase II GEOMETRY mono-1 study)[73]. Ninety-severn patients with *MET* exon 14 were enrolled and the primary efficacy endpoint was the ORR assessed by the Blind Independent Review Committee (BIRC). The results showed that the ORR was 68% and 41%, the DCR was 96% and 78%, the DoR was 12.6 and 9.7 months, and the PFS was 12.4 and 5.4 months in treatment-naïve and previously-treated patients, respectively[73]. A total of 14 patients in the study had brain metastases at baseline. Among the 14 patients, 13 (3 treatment-naïve and 10 previously-treated) were evaluable for tumor assessment. Seven patients achieved a partial response (including 4 complete responses), while 12 had stable disease.

Capmatinib demonstrates preliminary efficacy in NSCLC patients with *MET* primary amplification, especially among those NSCLC patients with a high GCN. In the OMETRY mono-1 study, 15 treatment-naïve patients had a *MET* GCN ≥ 10 and 69, 42, 54, and 30 previously-treated patients had a *MET* GCN ≥ 10, 6–9, 4–5, and < 4, respectively. The ORR was 40%, 29%, 12%, 9%, and 7%, the median DOR was 7.5, 8.3, 24.9, 9.7, and 4.2 months, and the median PFS was 4.2, 4.1, 2.7, 2.7, and 3.6 months among the corresponding cohorts, respectively.

Capmatinib has also been evaluated in combination with first- and third-generation EGFR-TKIs for NSCLC patients with acquired resistance to EGFR-TKIs and *MET* amplification or MET overexpression. In these patients, capmatinib combined with gefitinib preliminarily showed antitumor activity, especially in the high *MET* amplification group (GCN ≥ 6: ORR = 47%; mPFS = 5.5 months), whereas in

MET-overexpressing patients (IHC 3+) the efficacy was slightly inferior (ORR = 32%, median PFS = 5.45 months)[68]. When capmatinib was administrated in combination with nazartinib, the ORR was 43.5% and 27.9%, the DoR was 6.3 and 9.3 months, the PFS was 7.7 and 5.5 months, and the OS was 18.8 and 17.2 months in patients with EGFR-TKI resistance and *MET* amplification (GCN ≥ 4) or MET overexpression (IHC 3+) and in those with negative MET alterations, respectively[90].

Capmatinib has shown good overall safety and tolerability, with the most common adverse reactions being peripheral edema, nausea, vomiting, and increased blood creatinine, most of which were grade 1 or 2. The study enrolled 15 Chinese patients, who achieved an ORR of 53.3%. Although the DOR, PFS, and OS have not been reached, the safety profile was consistent compared to the overall population[91]. However, capmatinib caused interstitial pneumonia in 4.8% of patients, of which 1.9% was grade ≥ 3 and 1 death was reported[92].

The overall ORR was 20% in NSCLC patients with MET alterations (IHC 2+/3+, H-score ≥ 150, or *MET*/CEP ≥ 2.0, GCN ≥ 5, or EGFR wild type and IHC 3+, $n = 55$) treated with capmatinib, reaching up to 47% in patients with a GCN ≥ 6 ($n = 15$). The median PFS was up to 9.3 months[47].

Tepotinib

Tepotinib is an oral, highly selective type IB MET-TKI.

The VISION study[93] was a phase II clinical study that investigated the efficacy and safety of tepotinib in metastatic NSCLC with *MET* exon 14. The VISION study[93] enrolled 152 *MET* exon 14-positive patients to receive tepotinib (500 mg PO QD), among whom 99 had a follow-up duration > 9 months and were included in the efficacy analysis. The overall ORR (IRC-assessed) was 46.5% (44.2%, 48.5%, and 47.8% as the first-, second-, and third or above-line therapy, respectively). The median DoR, PFS, and OS were 11.1, 8.5, and 17.1 months, respectively. In recently updated data[94], the VISION study enrolled 313 *MET* exon 14-positive patients in cohorts A and C, who were followed for > 35 and > 18 months, respectively. The overall efficacy was generally consistent with the efficacy reported for the first time. The median DoR, PFS, and OS increased with a prolonged duration of follow-up and the ORR (IRC-assessed) was 51.4% (44.2%, 48.5%, 48.2%, and 47.8% as the first-, second-, second or above-, and third or above-line therapy, respectively). The median DoR, PFS, and OS were 18, 11.2, and 19.6 months, respectively. The ORR was 57.3% and the median DoR, median PFS, and median OS were 46.4, 12.6, and 21.3 m, respectively, in treatment-naïve patients. The ORR was 45% and the median DoR, median PFS, and median OS were 12.6, 11, and 19.3 months, respectively, in previously-treated patients. The ORR in intracranial lesions was 66.7%, the overall ORR was 56.1%, and the median DoR, PFS, and OS were 9, 8.5, and 17.5 months, respectively, in 15 patients with brain metastases at baseline.

Tepotinib achieved an ORR of 41.7%, a median DoR of 14.3 months and a median PFS of 4.2 months in the 24 patients with *MET* amplification (*MET* GCN ≥ 2.5 by NGS) included in the VISION study. Tepotinib has also been investigated in multiple studies for populations with *MET* secondary amplifications. Tepotinib combined with gefitinib was significantly more effective than chemotherapy in patients with acquired resistance to EGFR-TKIs (ORR: 67% *vs.* 42.9%; PFS 16.6 *vs.* 4.2 months, HR = 0.13, 90% CI = 0.04–0.43; OS: 37.3 *vs.* 13.1 months, HR = 0.08, 90% CI = 0.01–0.51) in the randomized, controlled, phase II INSIGHT study[95]. Forty-three patients achieved a PR, the ORR was 43.9%, and the median PFS was 5.4 months among 98 patients with positive FISH tests (*MET* GCN ≥ 5 and/or *MET*/CEP7 ≥ 2) in the INSIGHT2 study in which the efficacy and safety of tepotinib was assessed in the *MET*-amplified population with resistance to first-line osimertinib.

The most common adverse reactions to tepotinib were peripheral edema, nausea, diarrhoea, and increased blood creatinine, most of which were grade 1 or 2, demonstrating good overall safety and tolerability with manageable and controllable adverse reactions. One patient died of respiratory failure due to interstitial lung disease (ILD), which was considered related to tepotinib by the investigator.

Savolitinib

Savolitinib, a highly selective type IB MET-TKI, is the first approved type Ib MET inhibitor with independent intellectual property rights in China.

A Chinese multicenter, open-label, single-arm phase II clinical trial (HMPL-504) enrolled a total of 70 patients (including 25 patients with pulmonary sarcomatoid carcinoma) with unresectable or metastatic NSCLC with *MET* exon 14 to evaluate the efficacy, safety, and pharmacokinetics of savolitinib (600 mg po QD for patients with a body weight ≥ 50 kg and 400 mg po QD for patients with a body weight < 50 kg)[96,97]. Among the 70 patients, 42 (60%) received at least 1 prior systemic treatment, 28 (40%) were

naïve, 8 were treated with savolitinib (400 mg), and the remaining patients were treated with savolitinib (600 mg). The efficacy results showed that the overall ORR (IRC-assessed) was 42.9%, the DCR was 82.9%, and the median DoR, median PFS, and median OS were 8.3, 6.8, and 12.5 months, respectively. Savolitinib showed consistent benefits across subgroups. Specifically, the ORR was 40% and 44.4%, the median DoR was 17.9 and 8.3 months, the median PFS was 5.5 and 6.9 months, and the median OS was 10.6 and 17.3 months for pulmonary sarcomatoid carcinoma and other NSCLC histologic subtypes, respectively. The ORR was 46.4% and 40.5%, the median DoR was 5.6 and 9.7 months, the median PFS was 5.6 and 6.9 months, and the median OS was 10.9 and 19.4 months for treatment-naïve and previously-treated patients, respectively. Brain metastases were not selected as the target lesion in the efficacy assessment by IRC. Among the 3 patients in whom brain metastases were selected as the target lesion by the investigator, the intracranial lesions achieved a tumor response, and the median OS was up to 17.7 months in patients with brain metastases at baseline. The research team presented the data from a confirmatory, single-arm, multicenter, phase IIIb study at the 2023 World Conference on Lung Cancer[98]. In this study 87 treatment-naïve NSCLC patients with *MET* exon 14 were enrolled and 84 patients were included in the efficacy assessment by IRC with an ORR of 59.5%, a DCR of 95.2%, and a median PFS of 12.6 months; the DoR and the median OS have not been reached.

The TATTON study was a multi-cohort, multicenter, phase Ib study to evaluate the efficacy and safety of savolitinib combined with osimertinib in patients with previously treated EGFR mutation-positive lung cancer with *MET* amplification. The combined treatment showed an ORR of 33%–67% and a PFS, DoR, and OS of 5.5–11.1, 9.5–11, and 18.8–30.3 months, respectively, across cohorts. In patients with third-generation EGFR-TKI resistance and *MET* amplification, the ORR was 30% and the PFS was 5.5 m[53]. The SAVANNAH study is an ongoing, randomized, single-arm, global multicenter, phase II clinical trial to evaluate the efficacy of savolitinib combined with osimertinib in patients with locally advanced or metastatic NSCLC who have progressed on osimertinib. Partial data from the SAVANNAH study were published by Whampoa in 2022. The available results showed that among all patients with high MET levels (IHC 90+ and/or FISH 10+), the ORR was 49%. In patients with high MET levels who had not received chemotherapy, the highest ORR was 52%. In patients who did not have high MET levels, the ORR was 9%.

The most common adverse reactions to savolitinib were peripheral edema, nausea, and elevated hepatic enzymes; drug-induced ILD was not reported.

Glumetinib

Glumetinib (SCC244) is a potent and highly selective small molecule type Ib MET inhibitor. The pivotal phase II GLORY study was an open-label, international multicenter phase II clinical study to investigate the efficacy and safety in patients with locally advanced or metastatic NSCLC with *MET* exon 14 who had received ≤ 2 prior systemic treatments or no prior systemic treatment[99]. In this study 84 Chinese and Japanese patients were enrolled and received glumetinib (300 mg po QD), of whom 79 were included in the efficacy analysis, including 44 treatment-naïve and 35 previously-treated patients. The efficacy results showed that the primary endpoint ORR assessed by BIRC was 66% (71% in the treatment-naïve population and 60% in the previously-treated population), the secondary endpoint DCR was 84% (89% in the treatment-naïve population and 77% in the previously-treated population), the median DoR was 8.3 months (15 months in the treatment-naïve population and 8.2 months in the previously-treated population), the median PFS was 8.5 months (11.7 months in the treatment-naïve population and 7.6 months in the previously-treated population), and the median OS was 17.3 months (not reached in the treatment-naïve population and 16.2 months in the previously-treated population). The efficacy benefit trends were consistent across preset subgroups. A total of 14 patients had brain metastases at baseline. Thirteen patients were evaluable for efficacy and the ORR assessed by BIRC (intracranial lesions were not selected as the target lesion) was 85%. Five patients with brain metastases were selected as the target lesion by the investigator and all achieved intracranial objective responses. A total of 98% of patients receiving glumetinib experienced adverse reactions, of which approximately half were grade > 3 in severity. The most common adverse reactions were edema, hypoproteinaemia, headache, and decreased appetite. Among the adverse reactions, headaches were a relatively specific adverse reaction.

Vebreltinib

Vebreltinib (formerly bozitinib APL-101/PLB-1001, CBT-101) is a highly selective type IB MET-TKI. The multicenter phase II KUNPENG study[100,101] enrolled a total of 52 patients with

locally advanced or metastatic advanced NSCLC with *MET* exon 14 to receive vebreltinib (200 mg po BID). As of 9 August 2022 the efficacy results showed that the BIRC-assessed ORR was 75% (77.1% in the treatment-naïve population and 70.6% in the previously-treated population), the DCR was 96.2%, the median DoR was up to 15.9 months (16.5 months in the treatment-naïve population and 15.3 months in the previously-treated population), the median PFS was up to 14.1 months (14.5 months in the treatment-naïve population and 7.7 months in the previously-treated population), the overall median OS was 20.7 months (20.3 months in the treatment-naïve population and 20.7 months in the previously-treated population), and the median time-to-response (TTR) was 1.0 month. Subgroup analysis showed that lung cancer patients with baseline brain or liver metastases or old age (≥ 75 years) all benefited from treatment with vebreltinib with ORRs of 100.0%, 66.7%, and 85.7%, respectively. In 12 patients with *MET* amplification, the ORR was up to 100%[100].

In addition, vebreltinib was also investigated in populations with primary *MET* amplification. Cohorts 2 and 3 of the KUNPENG study included patients with primary *MET* amplification who had failed standard treatment and treatment-naïve patients with primary *MET* amplification, respectively. As of 14 May 2024, 33 and 53 patients were enrolled in cohorts 2 and 3, respectively, and a total of 80 patients were included in the efficacy-evaluable analysis set. The results showed a BIRC-assessed ORR up to 52.5% (53.3% in the previously-treated cohort and 52.0% in the treatment-naïve cohort), a DCR of 83.8% (86.7% in the previously-treated cohort and 82.0% in the treatment-naïve cohort), a median TTR of 0.95 months (1.05 months in the previously-treated cohort and 0.95 months in the treatment-naïve cohort), a median DoR of 11.1 months (11 months in the previously-treated cohort and 11.1 months in the treatment-naïve cohort), a median PFS of 8.3 months (7.4 months in the previously-treated cohort and 8.3 months in the treatment-naïve cohort), and a 12-month PFS rate of up to 35.8%. The FAS analysis showed a median OS of 13.2 months (11.2 months in the previously-treated cohort and 15.5 months in the treatment-naïve cohort). Vebreltinib had good overall safety with the most adverse reactions in grades 1 and 2 and the most common adverse reactions were peripheral edema, hypoproteinemia, and anemia.

Ensartinib

Both crizotinib and ensartinib are type Ia MET inhibitors that compete at the specific sites of multiple MET kinases, including Y1230 and G1163. Crizotinib has been investigated and demonstrated preliminary efficacy in populations with *MET* exon 14 and *MET* amplification.

In the PROFILE1001 study 65 patients in the cohort with *MET* exon 14 received crizotinib and were evaluable for efficacy. The results showed an ORR of 32%, including 3 patients with a complete response and a median PFS, median DoR, and median OS of 7.3, 9.1, and 20.5 months, respectively[102].

In the PROFILE1001 study, 38 patients with a primary *MET* amplification and a *MET*:CEP7 ratio ≥ 1.8 received crizotinib and were tested by FISH[103]. Twenty-one patients with high *MET* amplification (a *MET*:CEP7 ratio ≥ 4), 14 patients with moderate amplification (a *MET*:CEP7 ratio > 2.2 and a *MET*:CEP7 ratio < 4), and 3 patients with low amplification (a *MET*:CEP7 ratio ≥ 1.8 and a *MET*:CEP7 ratio ≤ 2.2) had ORRs of 8/21 (38.1%), 2/14 (14.3%), and 1/3 (33.3%), a median DOR of 5.2, 3.8, and 12.2 months, and a median PFS of 6.7, 1.9, and 1.8 months, respectively. In two other studies[104,105], after crizotinib treatment the ORR was only 27% in the population with moderate-to-high *MET* amplification (a *MET*:CEP ratio > 2.2) and only 16% in the population with high amplification (a *MET*:CEP ratio × 6.0).

Ensartinib is a second-generation ALK inhibitor that overcomes crizotinib-induced resistance mutations and has significant intracranial antitumor activity. Ensartinib also has some inhibitory effect on *MET* exon 14. In a study published by Xia et al.[106], 29 *MET* exon 14-positive patients treated with ensartinib achieved an ORR up to 69% and a median PFS and DoR of 6.1 and 6.8 months, respectively. A recent phase II trial further confirmed the activity of ensartinib in *MET* exon 14-positive NSCLC, showing an ORR of 53.3%, a DCR of 86.7%, an mPFS of 6.0 months, and a median DoR of 7.9 months[107]. The toxicity profile differs from type Ib MET inhibitors, which is an essential addition to the MET field. However, neither crizotinib nor ensartinib has been approved for use in patients with MET-altered NSCLC. Efficacy of anti-MET agents in NSCLC with MET alterations is listed in **Table 3**.

Choice other than sMETi

In addition to MET-TKIs, bispecific antibodies and antibody-drug conjugates (ADCs) targeting MET have also made some breakthroughs in recent years.

Bispecific antibodies targeting MET

Amivantamab Amivantamab is an EGFR-MET bispecific antibody used to treat advanced NSCLC with an EGFR exon

Table 3 Efficacy of anti-MET agents in NSCLC with MET alterations

Class	Drug	Study	Number of patients	MET alterations	ORR, %	Median PFS, months	Median OS, months
Type Ia TKI	Crizotinib	PROFILE1001	65 (evaluable)	*MET* exon 14	32%	7.3	20.5
	Ensartinib	ChiCTR2100048767	31	*MET* exon 14	53.3	6.0	NR
Type Ib TKI	Capmatinib	GEOMETRY mono-1	97	*MET* exon 14	NR	NR	NR
			28 1L		68	12.4	NR
			69 2L+		41	5.4	NR
	Tepotinib	VISION	313	*MET* exon 14	51.4	11.2	19.6
			164 1L		57.3	12.6	21.3
			149 2L+		45	11	19.3
	Savolitinib	NCT02897479	70	*MET* exon 14	42.9	6.8	12.5
			28 1L		59.5*	12.6	10.9
			42 2L+		40.5	6.9	19.4
	Gumarontinib	GLORY	79	*MET* exon 14	66	8.5	17.3
			44 1L		71	11.7	NR
			35 2L+		60	7.6	16.2
	Vebreltinib	KUNPENG	52	*MET* exon 14	75	14.1	20.7
			35 1L		77.1	14.5	20.3
			17 2L+		70.6	7.7	20.7
Antibody	Amivantamab	CHRYSALIS monothrapy cohort	97	*MET* exon 14	33	/	/
			16 1L		56	/	/
			28 METi-naive		46	/	/
			53 pretreated with METi		19	/	/
		CHRYSALIS combination cohort	36	Osimertinib-relapsed without biomarker selection	36	4.9	NC
			10	Osimertinib-relapsed with c-Met overexpression	90%	12.5	NC
	Sym015	NCT02648724	45 (20 evaluable)	*MET* exon 14 or MET amplification (GCN > 5)	25	5.5	/
	MCLA-129	NCT04868877	79	*MET* exon 14	11.5–43.5	/	/
			30 pretreated with METi		14.3–37.5	/	/
	CKD-702	NCT04667975	24	Not selected for MET alteration	20.8	/	/
			6	*MET* exon 14	50	/	/
ADC	Telisotuzumab Vedotin	LUMINOSITY	52	c-Met overexpression	36.5	/	/

20 insertion mutation. Amivantamab is the first EGFR/cMET bispecific antibody approved for marketing worldwide and was approved by the FDA for NSCLC with an EGFR exon 20 insertion mutation progressing after platinum-based chemotherapy in May 2021 based on the phase Ib clinical data. Several clinical studies involving amivantamab in EGFR TKI-resistant populations are also ongoing. In the phase I CHRYSALIS study, the overall ORR was 33% among the cohort with *MET* exon 14 [n = 97 (46% in patients who had not previously received METi) and n = 28 (19% in patients who had previously received METi)] and the median DoR was 11.2 months. The common adverse events included rash, infusion-related reactions, and paronychia[108]. The combination treatment cohort of the CHRYSALIS study investigated the use of amivantamab combined with lazertinib in patients with osimertinib-resistant, EGFR mutation-positive advanced NSCLC with a combined H-score ≥ 400 for EGFR/MET expression by IHC in a total of 10 patients, of whom 9 patients achieved a partial response with a median DoR of 9.7 months and a median PFS of 12.5 months[109]. Infusion-related reactions were a prominent adverse reaction to amivantamab. The PALOMA-3 study[110] was an international multicenter phase III clinical study to evaluate the pharmacokinetics, efficacy, and safety of subcutaneous (SC) *vs.* intravenous (IV) amivantamab combined with lazertinib in patients with EGFR-mutated advanced NSCLC after resistance to first-line treatment. The study results suggested that amivantamab (SC and IV) showed similar pharmacokinetics and ORRs in resistant EGFR + mNSCLC patients, while amivantamab SC showed better benefits in DoR and PFS and a significantly better benefit in OS. Amivantamab SC had lower incidences of infusion-related reactions (13% *vs.* 66% in the IV group) and venous thromboembolism (VTE).

ADCs targeting MET

Telisotuzumab vedotin Telisotuzumab vedotin [Teliso-V (ABBV-399)], an ADC targeting c-Met, is composed of an anti-c-Met humanized monoclonal antibody (ABT-700), a cleavable valine-citrulline linker and a tubulin inhibitor MMAE payload. Teliso-V shows therapeutic potential in NSCLC patients with c-Met overexpression. In a phase I/Ib study Teliso-V monotherapy showed good tolerability and antitumor activity in NSCLC patients,with an overall ORR of 23%, a median DoR of 8.7 months, and a median PFS of 5.2 months[111]. The phase II LUMINOSITY study[112] further evaluated the efficacy of Teliso-V monotherapy with c-Met overexpression defined as IHC ≥ 25% 3+ (highly expressed, ≥ 50% 3+; moderately expressed, 25%–50% 3+) for the non-squamous cohort and IHC ≥ 75% 1+ for the squamous cohort. In the non-squamous EGFR wild-type cohort, Teliso-V showed an ORR of 28.6% (highly expressed: 34.6%, moderately expressed: 22.9%), a median DOR of 8.3 months (highly expressed: 9.0 months, moderately expressed: 7.2 months), a median PFS of 5.7 months (highly expressed: 5.5 months, moderately expressed: 6.0 months), and a median OS of 14.5 months (highly expressed: 14.6 months, moderately expressed: 14.2 months). The ORR in the non-squamous EGFR mutant and squamous cancer cohorts was 11.4% (highly expressed: 16.7%, moderately expressed: 0%) and 10.7%, respectively. A global, open-label, randomized phase III trial is ongoing to evaluate the efficacy and safety of Teliso-V *vs.* standard treatment with docetaxel in patients with c-Met OE, wild-type EGFR, NSQ, and a/mNSCLC[113].

Chemotherapy

Before the advent of targeted therapy and immunotherapy, chemotherapy was the standard treatment option for patients with advanced NSCLC. Platinum-based doublet chemotherapy achieved a 1-year survival rate of 30%–40%. Currently, first-line chemotherapy is mainly used in patients who are not candidates for targeted therapy or immunotherapy. A retrospective study[114] showed that only 1 (9%) patient achieved a partial response after chemotherapy among 11 NSCLC patients with *MET* exon 14 and a median time-to-treatment discontinuation of 2.8 months. A systematic retrospective analysis of 39 studies involving 3989 NSCLC patients[115] revealed that in NSCLC patients with *MET* exon 14, the ORR was 50.7%–68.8% in patients receiving targeted therapy (MET-TKIs) and 23.1%–27.0% in patients receiving chemotherapy. Patients receiving chemotherapy had a significantly lower ORR than patients receiving targeted therapy. In another report from Korea[116], the median PFS and OS of first-line chemotherapy in NSCLC patients with *MET* exon 14 were 4.0 and 9.5 months, respectively, with an ORR of 33.3% in patients receiving pemetrexed-containing chemotherapy regimens (n = 12). The analysis of a study of 850 East Asian lung cancer patients[117] showed that the median OS was only 6.7 months after conventional chemotherapy in 18 NSCLC patients with *MET* exon 14. A retrospective analysis of 148 NSCLC patients with *MET*

exon 14 in the United States[118] showed patients who did not receive MET inhibitors (87.5% receiving chemotherapy and 12.5% receiving immunotherapy) had a significantly lower OS than patients who received MET inhibitors (8.1 months *vs.* 24.6 months). To date there are few data on chemotherapy in NSCLC patients with *MET* gene mutations, most of which were small retrospective studies. Based on the available data, chemotherapy has limited efficacy in NSCLC patients with *MET* gene mutations compared to selective MET TKIs, although there is a reported tumor response.

Whether chemotherapy combined with PD-1/PD-L1 inhibitors is the best therapy for NSCLC with MET alterations

Targeted therapy is the preferred treatment option for driver gene-positive NSCLC compared to ICIs, which has been demonstrated in EGFR-mutated, ALK-positive NSCLC patients. Unlike the above targets, *MET* exon 14-altered patients usually have a history of cigarette smoking and a significant number of patients are positive for PD-L1 expression, which makes the correlation between *MET* exon 14 mutation status and immunotherapy effect more complex.

The results of multiple studies[119,120] showed that there is no clear correlation between ICI efficacy and PD-L1 expression status in MET-altered NSCLC patients.

Chemotherapy combined with immunotherapy is less effective than driven gene therapy in first-line studies of NSCLC with MET alterations. As reported by Furqan et al.[121], a real-world study analysis of 287 advanced NSCLC patients with definite *MET* exon 14 showed that patients with *MET* exon 14 receiving capmatinib as first-line treatment had a higher real-world ORR (rwORR), longer real-world PFS (rwPFS), and OS compared to platinum-based chemotherapy, ICI monotherapy, or immunotherapy combined with chemotherapy; the rwORR was 73.4%, the rwPFS was 68% at 18 months, and the OS was 92.6% at 18 months.

Among first-line studies involving patients with NSCLC and MET alterations, ICI monotherapy was inferior to other first-line therapies. Leighl et al.[122] conducted a real-world analysis of 138 advanced NSCLC patients with *MET* exon 14 divided into high, low, absent, and unknown PD-L1 expression groups according to the tumor proportion score (TPS). The most common first-line regimen was ICI monotherapy, immunotherapy combined with chemotherapy, and chemotherapy alone for the high, low, and negative PD-L1 expression groups, respectively. In the high PD-L1 expression group, ICI monotherapy was less effective with a shorter median PFS and median OS than other first-line regimens (median PFS: 4.1 months *vs.* 5.4 months; median OS: 11.4 months *vs.* 17.0 months). No PFS and OS data were reported for first-line METi therapy in patients with high PD-L1 expression.

A prospective exploratory analysis[123] showed no significant differences in the ORR, PFS, and OS in patients receiving nivolumab regardless of *MET* amplification. In contrast, patients with high-level MET gains had a better ORR than patients with low-level MET gains.

In a phase II, multicenter, open-label clinical trial[124] to investigate the therapeutic effect of capmatinib combined with PD-1, advanced lung cancer patients without EGFR gene mutations who progressed on the first systemic treatment received capmatinib combined with PD-1. Patients participating in the study were first assessed for *MET* mutations and divided into high- and low-MET groups. The results showed that patients benefited from the two drugs regardless of MET mutation status, even patients without MET mutations.

Treatment strategies for NSCLC with acquired MET alterations

Acquired MET alterations have emerged as an important resistance mechanism to EGFR-TKI therapy in NSCLC patients with EGFR-sensitive mutations through high affinity for RTKs and sustained activation of RTK signaling pathways[125]. Acquired *MET* amplification is one of the most common acquired resistance alterations and is currently being investigated as a therapeutic target in some studies. Whereas targeted therapy for MET may also lead to acquired resistance by acquired point mutations in MET, this further increases the therapeutic and diagnostic challenges[126].

According to previous studies, MET-TKIs [tepotinib or capmatinib (INC280)] combined with gefitinib have achieved good responses and prolonged PFS in populations with acquired *MET* amplification. Sun et al.[127] compared the efficacy of chemotherapy combined with bevacizumab, MET-TKIs, and EGFR-TKIs in 9 NSCLC patients with acquired *MET* amplification and the results showed that chemotherapy combined with bevacizumab might benefit patients with EGFR-sensitive mutations and acquired *MET* amplification after EGFR-TKI failure and warranted further prospective studies with large samples.

Drug resistance and type II MET inhibitors

In addition to type I inhibitors, MET-TKIs include types II and III, depending on the mode of binding to MET kinase. Type II TKIs are also ATP-competitive and predominantly bind to the inactive conformations of MET kinases in a manner that may help overcome resistance caused by mutations in some MET kinase domains. Cabozantinib, merestinib, glesatinib, foretinib, and ANS014004 are all type II TKIs[128-130] that have been investigated in clinical trials in a variety of solid tumors and have shown some antitumor activity in patients with lung cancer and an ORR of 17.8% in NSCLC patients treated with foretinib[131] and up to 30% in NSCLC patients with *MET* mutations treated with glesatinib[130]. Unlike type I and II TKIs, type III TKIs bind to an allosteric site of MET kinase, induce conformational changes in the MET kinase, and thereby inhibit its activity[132]. To date no type II or III MET-TKIs have been approved for MET-altered NSCLC, but data suggest that the combination of type Ib and type II MET-TKIs can overcome the resistance produced by type Ib MET-TKIs.

Like other TKIs, patients receiving MET-TKIs may progress due to secondary resistance. The mechanisms of secondary resistance are generally divided into two categories (MET-dependent and -independent). MET-dependent resistance mainly includes secondary mutations in the MET kinase domain and amplification of the MET gene, which account for about one-third of all resistance cases. Mutations at positions H1094, G1163, L1195, D1228, and Y1230 of the *MET* gene and allelic amplification in exon 14 of *MET* have been shown to be associated with the resistance mechanisms to MET-TKIs, such as crizotinib and capmatinib. MET-independent resistance involves sustained activation of MET downstream signaling pathways, such as alterations associated with the RAS/MAPK and PI3K/AKT pathways and activation of bypass signaling pathways, including amplification or other mutations in genes, such as EGFR, BRAF, and KRAS[133].

Because type I/II MET-TKIs induce resistance by mutations at different loci, sequential or combined use of MET TKIs with different structures may become a therapeutic strategy to overcome MET-dependent resistance. Preclinical studies showed that glesatinib, a type II MET-TKI, overcame resistance caused by the Y1230H or Y1230S mutation. Foretinib, a type II MET-TKI, showed inhibitory effects on the capmatinib/tepotinib-induced Y1230X and D1228X mutations[134,135] and the combination of capmatinib and a type II MET-TKI (merestinib) inhibited the development of common resistance mutations[136]. Type II MET TKI ANS014004 bound to the inactive conformation (DFG-out) of MET in the ATP pocket by extension into the hydrophobic back pocket. *In vitro* studies showed that ANS014004 had superior antitumor activity against the *MET* Y1230H mutation and the *MET* D1228A mutation to cabozantinib and merestinib, suggesting that ANS014004 holds promise to overcome acquired resistance to type I MET TKIs. Clinical data have also confirmed the feasibility of this strategy. A phase II study showed that capmatinib had some efficacy in crizotinib-resistant patients with *MET* exon 14 mutation with an ORR of 10%, DCR of 80%, and mPFS of 5.5 months in 20 patients[137]. Several case reports have also suggested that cabozantinib can overcome resistance resulting from crizotinib-induced *MET* D1228N and D1246N mutations[138,139]. The combination of drugs targeting corresponding pathways is a feasible strategy against MET-independent resistance. Preclinical studies have demonstrated the excellent efficacy of dual inhibition of MET and other pathways in cell lines and/or xenograft models[133,140,141]. In the MET-2 cohort of the phase I CHRYSALIS study involving amivantamab, 19 patients with *MET* exon 14 mutations who progressed on MET-TKI therapy had an ORR of 21% on amivantamab[107]. In addition, sintilimab (an ICI) combined with chemotherapy ± bevacizumab significantly improved PFS compared to chemotherapy in EGFR-TKI-failed EGFR-positive non-squamous NSCLC[142,143]. This also provides some reference for MET-TKIs in the treatment of progressed NSCLC after resistance.

Toxicity management

MET TKIs have good overall tolerability with only a few patients discontinuing treatment due to adverse reactions. Common adverse reactions to MET-TKIs include peripheral edema, hypoalbuminemia, nausea, vomiting, and hepatic function abnormalities. However, each MET TKI currently marketed has a different spectrum of adverse reactions and for specific adverse reactions, targeted preventive, monitoring, and therapeutic measures should be taken. Given that *MET* exon 14 is more common in elderly patients who need more attention paid to adverse reaction management, we should properly manage adverse reactions caused by MET-TKIs by standardized diagnosis and treatment protocols and preventive measures.

Table 4 Expert consensus on the diagnosis and treatment of NSCLC patients with MET alterations

Classification	Serial No.	Consensus content	Recommendation level
Detection timing	Consensus 1	*MET* exon 14 detection is strongly recommended in advanced treatment-naïve or previously-treated NSCLC patients; *MET* gene amplification detection is strongly recommended for advanced NSCLC patients who are treatment-naïve or progressed after resistance to EGFR-TKIs or ALK-TKIs, etc. Exploratory detection for *MET* gene fusions and *MET* gene point mutations is recommended. Preventive detection for different types of MET alterations in histological samples is recommended in patients with early NSCLC by clinicians.	Strongly recommended
Detection method	Consensus 2	To detect *MET* exon 14, DNA-based NGS is preferred and RNA-based NGS can further improve the detection rate. Among the common methods to detect *MET* gene amplification, DNA-based NGS is preferred, followed by FISH, which is the gold standard for *MET* gene amplification detection.	Strongly recommended
Detection strategy	Consensus 3	It is preferred to detect *MET* variants using the histologic or cytologic samples of tumors on the DNA-based NGS platform incorporating *MET* gene detection. When DNA-based NGS results are negative, RNA-based NGS should be considered for complementary testing of the samples. IHC is used to screen MET overexpression using the histologic or cytologic samples of tumors. When histologic or cytologic evaluations of tumor samples are unavailable, liquid biopsy samples may be selected to detect *MET* gene mutations.	Strongly recommended
Detection quality control	Consensus 4	It is recommended to implement detections in laboratories that are certified by the College of American Pathologists (CAP) or Clinical Laboratory Improvement Amendments (CLIA), have passed the Good Clinical Laboratory Practice, or are accredited by *the* China National Accreditation Service for Conformity Assessment (CNAS) and other institutions or conform to relevant industry standards. In addition, due to the complex and diverse forms of *MET* exon 14, unified criteria and unclear thresholds for *MET* gene amplification and overexpression, active communication between clinicians and pathologists is recommended.	Strongly recommended
Results and interpretation	Consensus 5	The detection results should be scientifically classified and annotated according to the current bioinformatic analysis consensus and guidelines, and a standardized report should be issued. MTB interpretation is recommended for complex co-variation detection results.	Strongly recommended
Treatment	Consensus 6	Type Ib MET-TKIs are recommended for NSCLC with *MET* exon 14, and currently approved type Ib MET-TKIs include capmatinib, tepotinib, savolitinib, glumetinib, and vebreltinib, each of which has good efficacy, survival benefits, and intracranial efficacy in both treatment-naïve and previously-treated populations.	Strongly recommended
	Consensus 7	Novel drugs, including ADCs (e.g., telisotuzumab vedotin) and bispecific antibodies (e.g., amivantamab, MCLA-129), have also demonstrated good efficacy in MET-altered NSCLC patients, and some have also shown antitumor activity in patients who have progressed on prior METi; thus, we should encourage patients to participate in clinical studies.	Recommended
	Consensus 8	No specific drug is currently approved for the treatment of NSCLC patients with primary or secondary *MET* amplification. MET-TKIs alone or in combination with EGFR-TKIs have shown some efficacy, and high-level MET gains have shown some correlation with the efficacy.	Recommended
	Consensus 9	*MET* fusion and *MET* TKD mutations are relatively rare; limited case reports suggest they are sensitive to MET TKIs, such as crizotinib and capmatinib, and clinicians should continue to focus on the output of relevant evidence-based medical evidence to jointly promote standardized clinical treatment of this target.	Recommended

Table 4 Continued

Classification	Serial No.	Consensus content	Recommendation level
Resistance mechanisms	Consensus 10	Secondary resistance is the leading cause of disease progression in NSCLC patients treated with MET-TKIs, and its mechanisms include two major categories: MET-dependent and MET-independent. Based on accurate detection, investigators are exploring different treatment strategies, including using MET TKIs with different structures, MET-TKIs combined with targeted drugs of other pathways, and ICIs to overcome or delay the development of resistance.	Strongly recommended
Toxicity management	Consensus 11	Common adverse reactions to MET-TKIs include oedema, gastrointestinal toxicity, creatinine increased, hepatic enzyme increased, and ILD. Given that *MET* exon 14 is more common in elderly patients who need more attention paid to adverse reaction management, we should properly manage adverse reactions caused by MET-TKIs by standardized diagnosis and treatment protocols and preventive measures.	Strongly recommended

It should be noted that MET-TKI-induced edema may not be immediately symptomatic and the onset of adverse reaction edema varies between drugs. We should measure body weight early and prevent edema by wearing support stockings, elevating the foot of the bed, reducing salt intake, and encouraging patients to maintain daily activities and appropriately increase exercise. Once edema occurs, we should closely monitor the skin, avoid injury, and if necessary, use diuretics and lymphatic drainage.

The pathogenesis of hypoalbuminemia is unknown. Given the potential mechanism underlying hypoalbuminemia in NSCLC patients treated with MET TKIs, a high-protein diet alone may not be sufficient for control and albumin infusion or diuretics may provide transient benefit and/or prevent disease progression. A high-protein diet is unlikely to resolve hypoalbuminemia until the underlying cause is resolved. For grade ≥ 3 hypoalbuminemia, dose reduction or MET TKI interruption should be considered.

Management of rashes includes pre-dose evaluation, using mild emollients, sunscreen agents, and cleansing solutions, and avoiding long-time bathing or bathing in hot water to effectively protect and repair the skin barrier function and reduce the occurrence of skin adverse reactions to a certain extent. After evaluation combined with the specific rash types, targeted therapy should be adopted, treatment should be discontinued in a timely fashion or the dose should be reduced, drug metabolism and excretion should be promoted, initiate anti-inflammatory therapy in a timely fashion, prevent and treat infections, and strengthen supportive treatment and wound care.

In addition, we should promptly identify and manage specific adverse drug reactions. Headaches are a common and specific adverse reaction of glumetinib. Among patients receiving monotherapy with glumetinib (≥ 300 mg QD), headaches (mostly grade 1 or 2) occur in approximately 30% of tumor patients, mainly within 1–2 days of dosing. Only a few patients reduced the dose or discontinued the drug due to headaches and most patients completely recovered. ILD is a specific adverse reaction of tepotinib and there was one fatal case. Severe hypersensitivity is a specific adverse reaction to savolitinib.

Overall, through patient education, timely identification and active management of these adverse events, and continuous monitoring, we can effectively reduce the incidence of adverse reactions, then reduce the incidence of drug dose adjustment to maximize the potential therapeutic effects of the drugs.

Summary and prospect

Please refer to **Table 4** for expert consensus on the diagnosis and treatment of NSCLC patients with MET alterations. *MET*, a vital driver gene in NSCLC, has an important role in tumor development, progression, and metastasis through various activated forms, such as *MET* exon 14, *MET* amplification, overexpression, fusion, and mutation. Accurate identification of MET alteration type through molecular testing is essential for individualized and precise treatment[78]. For NSCLC with MET alterations, several new drugs have entered clinical practice, while others remain in the exploratory stage. Increasing understanding of the MET target is expected to advance treatment options for different MET alterations and guide the optimal sequencing of treatment regimens. Alas, there are new problems to be solved. First is the standardization of the testing. Second, except for *MET* exon 14, whether *MET* amplification and MET overexpression has a guiding role in clinical practice remains questionable and needs further investigation. Third, bottlenecks in efficacy, toxicity management, and how to overcome drug resistance are unmet clinical needs in the MET field. This expert consensus aims to continue focusing on the development of evidence-based medical insights, promote standardized diagnosis and treatment for NSCLC with MET alterations, and further improve survival outcomes for lung cancer patients.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Design of the expert consensus: Huijing Feng, Yang Xia, Wenxian Wang, Chunwei Xu and Qian Wang, Junping Zhang, Yong Song, Wenfeng Fang, and Yuanzhi Lu.

Conceived of the expert consensus and draft the expert consensus: Junping Zhang, Yong Song, Wenfeng Fang, and Yuanzhi Lu.

Coordinated with other authors: Junping Zhang, Yong Song, Wenfeng Fang, Yuanzhi Lu.

Discussion, read and approved the final manuscript: All authors.

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