

MET Crusaders is a community of Lung Cancer patients and care givers collaborating with advocates and medical professionals collectively dedicated to helping patients with a MET alteration live normal lives.

# **Come Join Us!**



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# Your resource for the latest research into the MET alteration.

CRUSADER NEWSLETTER

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# Top-level MET gene copy number gain defines a subtype of poorly differentiated pulmonary adenocarcinomas with poor prognosis

### Journal: Translational Lung Cancer Research

A variety of MET alterations can occur in non-small cell lung cancer (NSCLC), including MET amplification. This study aimed to quantify and define what it means to be MET amplified. A total of 373 patients with NSCLC were tested for their MET gene copy number (GCN). The data led to defining the top-level category for MET amplification as greater than the 90th percentile of the average GCN, or at least 10 MET gene copies per tumor cell on average. Data from trials with MET inhibitors have suggested that these inhibitors may have a "gene dose effect," suggesting that the GCN may play a role in response to inhibitors and survival outcomes. The authors of this study suggest it may be reasonable to give patients with MET top-level amplification earlier access to MET inhibitors by using it in the first line setting given the aggressive nature of MET top-level amplified NSCLC, though much further research is needed through prospective clinical trials to support this.

LINK TO ARTICLE

# Characteristics and Clinical Outcomes of Non-Small Cell Lung Cancer Patients in Korea with MET Exon 14 Skipping

Journal: In Vivo

This study assessed Korean patients with NSCLC and MET exon 14 skipping. A total of 1,020 patients were analyzed via next-generation sequencing, 20 of which were found to have MET exon 14 skipping (all negative for EGFR, ALK, ROS1, BRAF, and RET alterations). The median overall survival (OS) in patients who received first-line traditional platinum-based chemotherapy was 9.5 months, and progression-free survival (PFS) was 4 months. This illustrates poor clinical outcomes and low responses to therapy in these patients in the setting of many advancements and recent approvals of several MET inhibitors, emphasizing the need for screening for MET exon 14 skipping alterations in patients with NSCLC.

#### LINK TO ARTICLE

# Clinical and molecular correlates of PD-L1 expression in patients with lung adenocarcinomas

### Journal: Annals of Oncology

Programmed death-ligand 1 (PD-L1) is an FDA-approved biomarker that can help determine the body's response to antibody drugs like immune checkpoint inhibitors (ICIs). This article took a deeper dive into the molecular and clinical features of PD-L1 expression and how these features may help predict a patient's response to ICIs.

A total of 1,586 patients with lung adenocarcinoma had undergone PD-L1 testing. PD-L1 expression was significantly lower in primary tissue than metastatic tissue but did not significantly differ based on smoker status. PD-L1 was expressed at different levels depending on organ type. Among metastatic sites, PD-L1 expression was highest in lymph nodes and lowest in bone.

KRAS, TP53, and MET alterations were associated with high PD-L1 expression, while EGFR, STK11, and WNT alterations were associated with negative PD-L1 expression. Among the frequent gene alterations in lung adenocarcinomas, patients with MET alterations had the greatest proportion of PD-L1 high expression. These results demonstrate that there may be a correlation between levels of PD-L1 expression and existence of other molecular markers.



# Efficacy and Safety of Anti-PD-1 Immunotherapy in Patients With Advanced NSCLC With BRAF, HER2, or MET Mutations or RET Translocation: GFPC 01-2018

### Journal of Thoracic Oncology

The objective of this study was to determine the efficacy of immune-checkpoint inhibitors (ICIs) in 107 patients with metastatic NSCLC harboring BRAF, HER2, MET, or RET alterations. A total of 44 patients had a BRAF mutation, 23 had a HER2 mutation, 30 had a MET exon 14 skipping mutation, and 9 had a RET mutation. Programmed cell death ligand 1 (PD-L1) status was known in 70 patients, 34 of which were greater than or equal to 1% expression. These patients had received a median of one treatment prior to ICI.

Median duration of response was 15.4 months, progression-free survival (PFS) was 4.7 months, and overall survival (OS) was 16.2 months. Response rates varied based on alteration (BRAF: 26 to 35%, HER2: 27%, MET: 36%, RET: 38%). Of note, patients with MET exon 14 skipping were treated with either pembrolizumab or nivolumab, with a response rate of 35.7%, a median duration of treatment of 3.3 months, a median duration of response of 10.4 months, median PFS of 4.9 months, and median OS of 13.4 months.

Overall, this study demonstrated higher response rates in patients with MET exon 14 skipping compared to previous studies. This study concluded that ICI efficacy in patients with metastatic NSCLC and BRAF, HER2, MET, or RET alterations was similar to patients who did not harbor these alterations as shown in previous studies, but further studies are needed to confirm these findings.

# LINK TO ARTICLE

# Alterations in the PI3K Pathway Drive Resistance to MET Inhibitors in NSCLC Harboring MET Exon 14 Skipping Mutations

### Journal of Thoracic Oncology

This article emphasizes the prevalence of resistance to tyrosine kinase inhibitors (TKIs) for patients with NSCLC and MET exon 14 skipping mutations. Previous studies suggest response rates to targeted therapies like TKIs may be lower in patients with MET exon 14 skipping compared to other alterations, potentially due to this resistance.

As a result, this study looked at the phosphoinositide 3-kinase (PI3K) pathway, which is known to be connected to MET. They hypothesized that patients with PI3K pathway alterations and MET exon 14 skipping may have resistance to MET TKIs. They analyzed 65 patients with MET exon 14 skipping and assessed if they had any PI3K pathway alterations. They then used a cell line derived from a patient with known MET TKI resistance and cell lines from patients who had MET exon 14 skipping and a PI3K pathway alteration to assess sensitivity to a MET TKI (capmatinib, tepotinib, crizotinib, or foretinib) with or without a PI3K inhibitor (GDC0941).

The researchers found a phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) mutation in 2 of 65 samples (3%) and loss of phosphatase and tensin homolog (PTEN, which helps regulate PI3K pathway signaling) in 6 of 26 samples (23%). All 3 patients who were treated with a MET TKI (specific inhibitor not listed as patients were receiving through clinical trials) and had progression at their first clinical assessment after starting the MET TKI also had a PI3K alteration. Additionally, MET TKIs had no effect on cell lines that had both MET exon 14 skipping and a PI3K alteration.

Combining MET TKIs and PI3K inhibitors, caused inhibition of the PI3K pathway and restored sensitivity to MET TKIs. This reinforces that PI3K pathway alterations can occur in patients with NSCLC and MET exon 14 skipping and may contribute to MET TKI resistance. This suggests a potential role for PI3K inhibitors in this patient population in the future.



# Incidence and PD-L1 Expression of MET 14 Skipping in Chinese Population: A Non-Selective NSCLC Cohort Study Using RNA-Based Sequencing

### Journal: OncoTargets and Therapy

Previous studies have shown that MET exon 14 mutations occur in about 0.9%-4% of Asian patients with non-small cell lung cancer (NSCLC). These studies were based on DNA sequencing. These authors hypothesized that there could also be variations in RNA expression that would result in the same effect, but not detected by the DNA-based methods. The purpose of this study was to determine the prevalence of MET exon 14 mutations in an Asian population using RNA-based sequencing. In addition, the authors sought to determine the level of PD-L1 expression in patients with MET-mutated NSCLC, as this is a marker that predicts response to immunotherapy in other types of lung cancer.

RNA-based sequencing was performed on tumor samples from 951 patients with NSCLC who had undergone a biopsy or surgery for their lung cancer at two hospitals in China. Of these patients, 772 (81%) had the adenocarcinoma type and 166 (19%) had a different type of NSCLC. Overall, 16 patients (1.7%) had a MET exon 14 mutation. The prevalence was slightly higher (1.8%) among the subgroup of patients with adenocarcinoma. When patients with another driver mutation (EGFR, KRAS, ALK, ROS, RET) were excluded, the prevalence was 6.6%. Patients with a MET mutation were more likely to be over 60 years old compared to the overall population. More patients with a MET mutation had high PD-L1 expression (defined as  $\geq$ 50% of tumor cells staining positive) compared to patients without a MET mutation (69% vs 17%).

The prevalence of MET mutations determined by RNA sequencing was similar to other studies that used RNA sequencing in Western patients and similar to studies in Asian patients that used DNA sequencing. With the small number of patients and lack of a control group, it is difficult to make a conclusion on whether RNA sequencing was able to detect more mutations than DNA sequencing. Patients with MET mutations tended to be older and had higher PD-L1 expression than the general population. However, the clinical significance of higher PD-L1 expression in patients with MET-mutated NSCLC has not yet been determined.

# LINK TO ARTICLE

# High-level gain of mesenchymal-epithelial transition factor (MET) copy number using next-generation sequencing as a predictive biomarker for MET inhibitor efficacy

### Journal: Annals of Translational Medicine

The objective of this study was to determine an optimal MET copy number (CN) cut-off value in order to predict which patients with non-small cell lung cancer (NSCLC) and MET amplification would most likely benefit from MET inhibitors. They analyzed 40 samples from patients with NSCLC and determined the "adjusted copy number" or adCN to better predict which patients were more likely to respond to MET inhibitors.

The researchers found that 18 patients with an adCN greater than 13 had significantly longer progression-free survival (PFS) than those with an adCN less than 13. Patients with an adCN of less than 5.5 (low-level MET amplification) had a median PFS of 37.5 days, patients with an adCN of greater than 5.5 but less than 13 (intermediate-level MET amplification) had a median PFS of 84 days, and those with an adCN greater than 13 (high-level MET amplification) had a median PFS of 84 days, and those with an adCN greater than 13 (high-level MET amplification) had a median PFS of 84 days, and those with an adCN greater than 13 (high-level MET amplification) had a median PFS of 84 days, and those with an adCN greater than 13 (high-level MET amplification) had a median PFS that had not yet been reached during the study. This suggests that adCN is positively correlated with MET inhibitor efficacy and response in patients with NSCLC and MET amplification. As a result, adCN may be an adequate biomarker for predicting response to MET inhibitors in the future.



# Management of NSCLC Patients with MET Exon 14 Skipping Mutations

# Journal: Current Treatment Options in Oncology

This review article focuses on assessing future options for patients receiving MET tyrosine kinase inhibitors (TKIs) due to the potential for developing resistance, and how differentiating between generations of MET TKIs may help overcome this resistance.

This article divides MET TKIs into three different types based on where they bind to MET: type I, type II, and type III. Each of these types represents a different generation of medications. Type I inhibitors include crizotinib, capmatinib, tepotinib, and savolitinib. Type II inhibitors include cabozantinib, glesatinib, and merestinib. Type III inhibitors include tivantinib. Many of these inhibitors are currently being evaluated in patients with NSCLC and MET alterations in ongoing clinical trials.

Some case reports have indicated resistance to MET inhibitors, such as crizotinib, in patients with NSCLC and MET alterations. There are a variety of mechanisms of resistance reported, including decrease of mutation abundance, changing of the MET mutation site, as well as intrinsic or acquired resistance via pathways such as RAS and EGFR. These mechanisms represent both on-target and bypass pathways that lead to resistance. On-target mechanisms include mutations within MET as well as MET amplification. Bypass mechanisms include amplification in EGFR, HER2, HER2, and MAPK pathway genes such as KRAS and BRAF, as well as mutations in KRAS.

This review reinforces the importance of screening for MET alterations in patients with NSCLC in order to guide therapy. Some reports suggest switching from type I to type II MET TKIs may overcome resistance driven by the development of mutations within MET. The review encourages further exploration into sequential treatment with MET TKIs for on-target resistance, and EGFR-MET or MET-MEK combination therapy for bypass resistance in patients with NSCLC and MET exon 14 skipping. Further studies need to be conducted to assess primary and acquired resistance to MET TKIs in patients with MET exon 14 skipping.

### LINK TO ARTICLE

# Molecular Mechanisms of Acquired Resistance to MET Tyrosine Kinase Inhibitors in Patients with MET Exon 14-Mutant NSCLC

# Journal: Clinical Cancer Research

Although MET inhibitors can be effective treatments for MET-mutated non-small cell lung cancer (NSCLC), patients who initially responded to a MET inhibitor can develop resistance over time and stop responding to MET inhibitor therapy. The purpose of this study was to identify genetic changes associated with MET inhibitor resistance.

The study included 20 patients with MET exon 14-mutated NSCLC who had progressed while on MET inhibitor treatment (specific inhibitors not listed in abstract). Researchers identified genetic changes that could cause resistance in 15 of those 20 patients. These included mutations or overexpression of the MET kinase itself (7 out of 20 patients) and in other genes known to cause resistance such as KRAS, EGFR, HER3, and BRAF (9 out of 20 patients). For two patients who had mutations in the MET kinase itself, the oncologists switched from a type I MET inhibitor to a type II MET inhibitor and this produced a response.

This study suggests that both mutations in MET and mutations in other proteins or genes are implicated in resistance to MET inhibitor therapy. More information is needed on the types of mutations and how they might respond to a change in medication (for mutations in MET) or combination therapy (for additional mutations in other proteins or genes).



# MET Alterations Are a Recurring and Actionable Resistance Mechanism in ALK-Positive Lung Cancer

#### Journal: Clinical Cancer Research

ALK-positive lung cancers can develop resistance after treatment with ALK inhibitors. There have been reports of MET amplification being involved in the development of resistance to and subsequent progression on ALK inhibitors. This study performed next-generation sequencing on 207 samples from patients with ALK-positive lung cancer to detect MET alterations.

MET amplification and/or MET fusion was present in 15% of the patients who relapsed on next-generation ALK inhibitors, 12% who relapsed on second-generation ALK inhibitors (ceritinib, alectinib, brigatinib), and 22% who relapsed on the third-generation ALK inhibitor lorlatinib. Therefore, the frequency of MET amplification was highest in patients who developed resistance to lorlatinib. Patients treated in the first line setting with a second-generation ALK inhibitor were significantly more likely to develop MET amplification than patients treated with a next-generation ALK inhibitor after crizotinib (which targets both MET and ALK). Additionally, MET amplification was observed in one-third of patients who received a second-generation ALK inhibitor in the first line setting compared to less than 10% of patients treated with crizotinib in the first line setting.

Cell lines resistant to ALK with MET amplification or rearrangement were successfully resensitized to treatment when treated with both ALK and MET inhibitors. Additionally, two patients with ALK-positive lung cancer with MET alterations rapidly responded to combination therapy with an ALK and MET inhibitor. However, both patients relapsed after 3 months.

Given the highest rate of relapse and development of resistance occurred in patients treated with the third-generation ALK inhibitor lorlatinib, this may point to a potential relationship between inhibitor potency and likelihood of developing resistance. More studies are needed to assess ALK and MET inhibitor combinations, and to further characterize the relationship between MET and ALK inhibitor resistance.

LINK TO ARTICLE

# Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations (VISION Trial)

### New England Journal of Medicine

The objective of this phase 2 study was to determine the safety and effectiveness of a new MET inhibitor, tepotinib, among 152 patients living with advanced or metastatic MET exon 14-mutated NSCLC. Almost half of patients had received no prior treatments for metastatic disease, but a quarter of patients had been exposed to two or more prior treatments. All patients received tepotinib 500 mg orally once daily. The primary outcome was the objective response rate (ORR) for the 99 patients who had been followed for at least 9 months.

The authors found that nearly half of patients (46%) responded to tepotinib, experiencing between 75% and 99% reduction in their tumors. The time to progression was 8.5 months on average. Patients who were receiving tepotinib as their first treatment responded similarly to those who had received other treatments before tepotinib. Of the 11 patients with brain metastases, the response rate was 55%. Serious side effects occurred in about a quarter (28%) of patients, including leg and ankle swelling (7%), pancreas inflammation (3%), and fluid in the lungs (3%). About 1 in 10 patients had to stop treatment due to a side effect.

This trial showed that a significant portion of patients with advanced or metastatic MET exon 14-mutated NSCLC respond to tepotinib. These results led to the approval of tepotinib for this patient population in Japan.



# Therapeutic Efficacy of ABN401, a Highly Potent and Selective MET Inhibitor, Based on Diagnostic Biomarker Test in MET-Addicted Cancer

### Journal: Cancers

This study analyzed the efficacy of a MET inhibitor called ABN401 in cancer cell lines and mouse models with MET amplification, MET overexpression, and MET exon 14 skipping. They discovered that ABN401 is a highly potent MET inhibitor that is highly selective for MET. ABN401 also has low off-target activity due to its high selectivity, suggesting that the frequency of adverse effects may be low. Additionally, the researchers found that the effectiveness of ABN401 is directly correlated with the MET copy number (CN), MET expression level, and MET exon 14 skipping mutation. ABN401 is currently being evaluated in a phase I/II study to determine its safety and efficacy in humans.

### LINK TO ARTICLE

# Erlotinib plus tivantinib versus erlotinib alone in patients with previously treated stage IIIb/IV non-small-cell lung cancer: A meta-analysis based on randomized controlled trials

### Journal: Medicine

Previous studies have looked at the safety and effectiveness of adding tivantinib (a MET inhibitor) to erlotinib (an EGFR-inhibitor) in patients with previously treated non-small cell lung cancer (NSCLC). The results were different among these trials, so the authors of this study analyzed the combined data from these studies to gain a better understanding of the results.

The authors found five randomized controlled trials that met their criteria. These studies included 1522 patients with NSCLC who had received at least 1 prior treatment including platinum-based chemotherapy, and were not previously treated with an EGFR inhibitor. Importantly, the study included patients with both MET-mutated and non-MET-mutated cancers. Patients were randomized to erlotinib plus tivantinib (ET) or erlotinib plus placebo (EP).

ET was associated with longer progression-free survival (27% reduction in risk of progression or death) but no difference in overall survival. In patients with high MET expression (note: what constitutes high-level is undefined in this analysis), ET was associated with higher overall survival (24% reduction in risk of death). However, patients who received ET were 43% more likely to discontinue treatment due to a side effect compared to EP. ET was associated with more neutropenia (including febrile neutropenia) but less diarrhea.

ET seems more effective than EP, especially for patients with MET mutations. However, the results are difficult to apply for several reasons. First, this analysis included patients without EGFR or MET mutations, which is not consistent with current best practices. In addition, all patients in this trial experienced first-line chemotherapy, which is not typically recommended for patients with EGFR or MET mutations. The most important evidence in this trial is the safety information. ET is associated with more severe side effects, including greater febrile neutropenia, compared to erlotinib alone. For patients on both an EGFR inhibitor and a MET inhibitor, providers and patients should be aware of this risk and take appropriate precautions to make sure patients can receive this treatment safely.



# Tepotinib plus gefitinib in patients with EGFR-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): an open-label, phase 1b/2, multicentre, randomised trial

### Journal: The Lancet - Respiratory Medicine

This study assessed the safety and efficacy of tepotinib plus gefitinib in patients with advanced or metastatic non-small-cell lung cancer (NSCLC) who have an EGFR mutation and MET overexpression or amplification and had developed resistance to an EGFR inhibitor.

A total of 55 patients in phase 2 were analyzed. Patients were randomly assigned to receive tepotinib 500 mg once daily plus gefitinib 250 mg once daily or standard platinum doublet chemotherapy. Survival outcomes were similar between groups, with a median progression-free survival (PFS) of 4.9 months in the tepotinib and gefitinib group versus the standard chemotherapy group. Median overall survival (OS) was 17.3 months in the tepotinib and gefitinib group vs 18.7 months in the standard chemotherapy group.

PFS and OS were higher with tepotinib and gefitinib compared to standard chemotherapy in 34 patients with high levels of MET overexpression (PFS 8.3 months versus 4.4 months and median OS 37.3 months versus 17.9 months). Survival rates were also higher in 19 patients with high levels of MET amplification in the tepotinib and gefitinib group versus standard chemotherapy (median PFS 16.6 months versus 4.2 months and median OS 37.3 months versus 13.1 months).

The most frequent adverse effects (grade 3 or higher) in the tepotinib and gefitinib group were increased amylase (16%) and increased lipase (13%). The results of this study suggest improved anti-tumor activity with tepotinib and gefitinib compared to standard chemotherapy in patients with EGFR mutant NSCLC with MET amplification or overexpression.

### LINK TO ARTICLE

Response to Checkpoint Inhibition in Non-Small Cell Lung Cancer with Molecular Driver Alterations

### Journal: Oncology Research and Treatment

Previous studies have established that patients who have non-small cell lung cancer (NSCLC) with EGFR mutations do not respond well to immune checkpoint inhibitors (ICIs). However, the response of other driver mutations to ICIs is not well known. The goal of this study was to analyze the response of NSCLC with different driver mutations to ICIs.

This study was retrospective and included 84 patients with NSCLC in Germany who had received ICIs. Of the 51 patients with driver mutations, those who had PIK3CA, EGFR, or STK11 mutations did not respond. However, patients with KRAS, TP53, and MET exon 14 mutations responded well (specifics of response undefined in available abstract) to ICIs.

The authors concluded that molecular testing may be useful in guiding treatment decision making for patients with NSCLC. However, prospective studies with larger numbers of patients would be required to confirm the impact of these mutations on response to ICIs.



